

The Mastocytosis Society Survey on Mast Cell Disorders: Patient Experiences and Perceptions

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What is already known about this topic? Mastocytosis and mast cell activation syndromes are rare diseases or entities manifested by symptoms that mimic allergies, anaphylaxis, and chronic conditions, and can go unrecognized for many years with unnecessary suffering by patients.

What does this article add to our knowledge? This article provides the first description of the US mastocytosis and mast cell activation syndromes population based on a survey of patients. Results include the length of time to diagnosis, disease impact, symptoms, specific organ systems affected, and associated conditions, such as allergies and triggers.

How does this study impact current management guidelines? This article will provide clinicians with an evidenced-based rationale for a focused investigation of the wide range of symptoms and experiences of patients with suspected or confirmed mastocytosis and/or mast cell activation syndromes.

BACKGROUND: Mast cell diseases include mastocytosis and mast cell activation syndromes, some of which have been shown to involve clonal defects in mast cells that result in abnormal cellular proliferation or activation. Numerous clinical studies of mastocytosis have been published, but no population-based comprehensive surveys of patients in the United States have been identified. Few mast cell disease specialty centers exist in the United States, and awareness of these mast cell disorders is limited among nonspecialists. Accordingly, information concerning the experiences of the overall estimated population of these patients has been lacking.

OBJECTIVE: To identify the experiences and perceptions of patients with mastocytosis, mast cell activation syndromes, and related disorders, The Mastocytosis Society (TMS), a US based

patient advocacy, research, and education organization, conducted a survey of its members and other people known or suspected to be part of this patient population.

METHODS: A Web-based survey was publicized through clinics that treat these patients and through TMS's newsletter, Web site, and online blogs. Both online and paper copies of the questionnaire were provided, together with required statements of consent.

RESULTS: The first results are presented for 420 patients. These results include demographics, diagnoses, symptoms, allergies, provoking factors of mast cell symptoms, and disease impact.

CONCLUSION: Patients with mastocytosis and mast cell activation syndromes have provided clinical specialists, collaborators, and other patients with information to enable

has consultant arrangements with Merck, Novartis, and Genentech; and is

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Abbreviations used

AFIRMM- Association Française pour les Initiatives de Recherche sur le Mastocytes et les Mastocytoses
CM- Cutaneous mastocytosis
IA- Idiopathic anaphylaxis
Ig- Immunoglobulin
MC- Mast cell
MCA- Mast cell activation
MCAD- Mast cell activation disorder
MCAS- Mast cell activation syndrome
MCD- Mast cell disorder
RAST- Radioallergosorbent test
REMA- Red Española de Mastocitosis
SM- Systemic mastocytosis
TMEP- Telangiectasia macularis eruptiva perstans
TMS- The Mastocytosis Society, Inc
UP- Urticaria pigmentosa

them to explore and deepen their understanding of the experiences and perceptions of people coping with these disorders. © 2013 The Authors. Published by Elsevier

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Mature mast cells (MC) are found around blood vessels in all tissues and also where the body interacts with its surroundings, well positioned for quick reaction to environmental threats. MC disorders (MCD) include diseases that involve abnormal proliferation and/or activation of these cells. Patients may have primary MCD or other MC activation syndromes (MCAS),¹⁻⁴ sometimes referred to as MC activation disorders (MCAD). People with MCD may be at risk for anaphylaxis and chronic and debilitating symptoms. MCD terminology has evolved as researchers have gained new insights. Clonal MC carrying D816V or other KIT tyrosine kinase mutations have been identified in patients with primary MCD, including mastocytosis and monoclonal MCAS.^{1,2,4-6} Cutaneous mastocytosis (CM) usually occurs in children, whereas systemic mastocytosis (SM), which involves internal organs, is generally diagnosed in adults.

Criteria for diagnosing MC activation (MCA) have recently been proposed in a consensus report.² MCA occurs by both IgE-dependent and independent mechanisms, which cause MC to release mediators, including histamine, tryptase, arachidonic acid metabolites (eg, prostaglandins and leukotrienes), cytokines, and chemokines, which initiate or exacerbate symptoms. Primary MCAS is associated with MCA symptoms and the presence of World Health Organization criteria for SM.² MCA can also be present in mastocytosis and lead to reduced quality of life.² In other patients, an underlying allergy may be found to cause the MCA; these patients have secondary MCAS. Patients with MCA symptoms without defined clonal MC, or other underlying conditions that might lead to MCA, are diagnosed as having idiopathic MCAS.²

The Mastocytosis Society, Inc (TMS) (www.tmsforacure.org), a US-based patient organization, provides support, research, and advocacy for those patients with mastocytosis, MCAS, and

related disorders. This article describes a Web-based survey by TMS for people with these disorders. Demographics, diagnoses, symptoms, allergies and/or intolerances, provoking factors of MC symptoms, preventive carrying of epinephrine and/or medical identification, and disease impact on lives are reported. Additional concerns will be described in future reports.

METHODS

Study design

The cross-sectional survey questionnaire was developed by the TMS Research Committee (S.J., N.R., B.J.) and executive board members (V.S., L.S.) by using preliminary questions and advice provided by MC specialists (P.V., C.A.). A copy of the survey questionnaire is provided as [Figure E1](#) (in this article's Online Repository at www.jaci-inpractice.org). The survey was open to patients who identified themselves as having an MCD and who were not participating in a similar concurrent European Union survey. Caregivers were instructed to answer all questions for minors and other patients unable to answer for themselves.

Web site and database development. Survey questions were converted into an online format (B.J., S.J.). An external company hosted the Web survey, backed by an on-site-encrypted, secure database that was moved to a secure system for analysis after survey closure.

Survey population, recruitment, and data collection

Population. Patients of all ages, or patient caregivers, living in or outside the United States, with mastocytosis, MCAS and/or MCAD, or other MCDs were invited to complete the survey irrespective of TMS membership.

Publicity. The survey was publicized in the month before its posting through a TMS publication, *The Mastocytosis Chronicles*, notices in clinics of physicians who work with the society, support groups, the TMS Web site, and online MCD-related blogs.

Access. The survey was posted online through a TMS Web site link, between April 15 and May 24, 2010, with paper copies mailed upon request. Entry required checkbox selection that indicated respondents' understanding of survey confidentiality and procedures. After providing consent, the entrants received a unique and confidential user number and password, which allowed them to stop during the survey and return later. A "no charge" telephone number and e-mail address were posted for help with completing responses.

Data evaluation. Valid responders were defined as those who answered at least some questions beyond the opening section for Demographics and Diagnosis. Data evaluation was performed by using Excel and Access software (Microsoft Corp, Redmond, Wash). The variable "years until diagnosis" was calculated by subtracting the year of symptoms onset from the year of diagnosis. Some percentages do not sum to exactly 100% due to rounding. In certain cases, percentages less than 5% or missing responses are not reported.

When respondents selected multiple diagnosis options, they were classified as follows: urticaria pigmentosa (UP) or another form of CM, along with MCAS and/or MCAD or idiopathic anaphylaxis (IA), was classified as CM; UP plus SM was classified as SM; UP plus SM and MCAS and/or MCAD, was classified as SM. Those who marked both IA and MCAS and/or MCAD were classified in

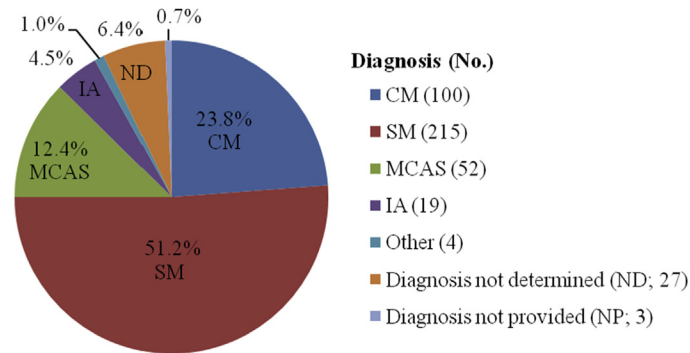


FIGURE 1. Reported diagnoses of 420 survey respondents, reporting each diagnosis type. “Diagnosis not determined” also includes those who were “not sure.”

the IA category. MCAS was reserved for those marking MCAS and/or MCAD who did not mark another mastocytosis category or IA.

RESULTS

Demographics

A total of 530 people entered the survey, of whom 41 did not answer any questions and 69 only completed the initial Demographics and Diagnosis section. Eliminating these groups yielded 420 valid responders. Most (370 [88.1%]) completed the survey for themselves. Because anonymity and confidentiality were assured, it is not possible to report proportion of members versus other responders nor their places of residence. However, care in the United States was received by 84.3% (317 of 376 respondents). There were 62.6% female respondents, 22.1% male respondents, and 15.2% not stated. Ages of 416 subjects who provided birth years ranged from 1 to 80 years with an average of 44.8 years and a median of 48 years. Most (393 [93.6%]) were white, with 6.0% Native American, Hispanic, or other ethnic or mixed groups.

Diagnoses

Diagnoses were determined (Figure 1) and reported as “confirmed by test results” by 89.5% of the 315 with CM or SM. Of 100 people who listed CM, 35 were younger than age 18 years, of whom just one listed having a bone marrow biopsy. Only 40% of the 65 adults with CM reported having this biopsy. Of 215 who reported SM (4 of whom were younger than age 18 years), 7.0% listed aggressive SM, 6.0% also noted an associated hematologic disorder, and one had MC leukemia (0.5%). Bone marrow biopsies were reported by 72% of the total SM group. Additional details on diagnoses can be found in the Online Repository. Years that elapsed between the first symptoms and the diagnosis for 341 people who provided these data ranged from less than 1 year to 50 years, with an average of 6.5 years and a median of 3 years.

Symptoms related to MCD

Severity (extreme, moderate, a little bit, or not at all) and frequency (daily, occasionally, rarely, or never) of 29 different MCD symptoms were queried and proportions with any severity (extreme, moderate, or a little bit) or moderate or extreme severity, in total or on a daily or occasional basis, are shown in Tables I and II. More than two-thirds of the respondents listed any severity of itching, flushing, fatigue, and stomach pain. More

than half also noted these symptoms daily or occasionally with moderate or extreme severity, with fatigue and stomach pain noted most frequently. Daily extreme severity of fatigue was experienced by 91 respondents (21.7%) and stomach pain by 62 (14.8%) (for this and other extreme severity symptom data, see Tables E1 and E2 in this article’s Online Repository at www.jaci-inpractice.org). Other notable symptoms included brain fog or cognitive difficulties, diarrhea, headache, joint pain, UP rash or telangiectasia macularis eruptiva perstans eruptions, light-headedness or syncope, abdominal bloating, anxiety, and bone and lower abdomen pain.

Allergies

Of the initial 420 participants, 384 (91.4%) answered questions about allergies. Most (255 [66.4%]) recalled having allergy testing, of whom 200 (78.4%) recalled a skin test either alone (87 [34.1%]) or in addition to a RAST or other unspecified allergy tests (114 [44.7%]). Forty-three people (16.9%) did not recall having a skin test but did recall having a RAST or other blood test with or without other allergy tests.

The survey queried participants on “allergies,” including testing results and whether those allergies “cause problems,” with or without a positive test. More than half of the 384 allergy section respondents (224 [58.3%]) reported drug allergies based on positive allergy tests (63 [16.4%]) and/or problems caused by drugs (142 [37.0%]). More than half (223 [58.1%]) reported allergies to environmental substances and/or inhalants; 154 tested positive (40.1%), and 163 noted that they caused problems (42.2%). Half (193 [50.3%]) reported food and beverage allergies, 89 reported a positive test (23.2%), and 146 noted problems caused by foods or beverages (38.0%). (Percentages of specific substances and categories listed by respondents for the above allergen types are presented in Tables E3-E5 in this article’s Online Repository at www.jaci-inpractice.org). Allergies to insect stings were reported by 109 people (28.4%); 54 recalled a positive insect venom allergy test (14.1%), and 93 noted that insect stings caused problems (24.2%). Some allergy section respondents (45 [11.7%]) reported a latex allergy; 18 recalled a positive test (4.7%), whereas 40 noted that they had problems with latex (10.4%). A positive allergy test for at least one allergen type that TMS queried was listed by 207 respondents (53.9%).

Allergen immunotherapy (“allergy shots”) was received by 82 allergy respondents (21.4%), of whom 47 tolerated this therapy (57.3%). However, only 21 who tolerated injections found them

TABLE I. Severity and frequency of skin and gastrointestinal symptoms among 420 respondents

Symptom	Severity			
	Any*		Moderate or extreme	
	Total responses, no. (%)	Daily or occasionally, no. (%)†	Total responses, no. (%)	Daily or occasionally, no. (%)‡
Skin				
Flushing	321 (76.4)	264 (82.2)	239 (56.9)	216 (90.4)
Itching	333 (79.3)	292 (87.7)	238 (56.7)	226 (95.0)
UP rash or TMEP eruptions	257 (61.2)	223 (86.8)	196 (46.7)	180 (91.8)
Darier sign	216 (51.4)	183 (84.7)	152 (36.2)	141 (92.8)
Dermatographism	222 (52.9)	176 (79.3)	133 (31.7)	122 (91.7)
Rashes, other than UP or TMEP	184 (43.8)	140 (76.1)	128 (30.5)	115 (89.8)
Gastrointestinal (other than pain)				
Diarrhea	277 (66.0)	237 (85.6)	220 (52.4)	203 (92.3)
Abdominal bloating	256 (61.0)	217 (84.8)	186 (44.3)	174 (93.5)
GERD	241 (57.4)	197 (81.7)	164 (39.0)	153 (93.3)
Nausea and vomiting	226 (53.8)	161 (71.2)	156 (37.1)	131 (84.0)

GERD, Gastroesophageal reflux.

*Any severity: extreme, moderate, or a little bit.

†The percentage of the total with any severity.

‡The percentage of the total with moderate or extreme severity.

helpful (44.7%), 17.0% did not, and 34.0% were not sure. A majority of the 57 survey participants who wrote of specific allergen immunotherapy types noted injections against inhalant and/or environmental allergens (47 [82.5%]), whereas 14% noted venom immunotherapy and 3.5% listed drugs. Although not standard for treatment of food allergies, 7.0% listed “allergy shots” for food immunotherapy.

Triggers and/or provoking factors

Common triggers for MCA symptoms were provided in a checklist, along with an open-ended “additional triggers” question. Of 382 remaining participants, 366 (95.8%) checked or listed triggers (Figure 2). Additional trigger details are listed in Table E6 (in this article’s Online Repository at www.jaci-inpractice.org). Insect stings were reported as triggers by 128 respondents, of whom, 93 had previously reported positive tests or problems with stings in the allergy section. Sixteen other participants who had previously noted positive sting allergy tests or problems did not report them as triggers. In total, 144 respondents (37.7%) listed insect stings as a trigger, recalled a positive insect sting allergy test, and/or noted in the Allergy section that they “caused problems.”

Self-injectable epinephrine and medical alert identification

More than three-fourths (305 [77.0%]) of 396 respondents had a prescription for self-injectable epinephrine, and 239 (60.4%) always carried the medication. More than half (193 [50.9%]) of 379 respondents carried medical alert jewelry or cards. Most (341 [90.0%]) were interested in carrying a regional or global identification card for MCD.

Living with an MCD

Most of the 379 respondents who answered the question about overall MCD emotional impact on their lives felt it impacted them either extremely (154 [40.6%]) or moderately (134 [35.4%]), whereas 15.6% noted its impact as a little bit, and 3.4% felt no impact. The greatest single distress-causing

aspect of living with an MCD was the unpredictability of symptoms (95 [25.1%]), followed by gastrointestinal symptoms (17.9%), an inability to work or to participate in daily living activities (15.3%), pain (12.9%), anaphylactic episodes (12.1%), fatigue (10.3%), and fear or anxiety (4.2%). Relative severity regarding coping with each aspect was ranked as extreme, moderate, a little bit, or not at all. The relative proportions of those affected extremely, moderately, or a little bit for each aspect of life with a MCD are illustrated in Figure 3. More than 60% of respondents were affected either moderately or extremely regarding their need for coping with unpredictability of symptoms, gastrointestinal problems, and fatigue.

Opinions on disease classification

Responses to questions regarding opinions on MCD classification are presented in the Online Repository.

DISCUSSION

Reports concerning patients with MCD have noted the mean time from symptom onset to diagnosis of nearly 3 and up to 9.5 years,⁷⁻⁹ and this duration also was extensive for TMS survey respondents (mean, 6.5 years; median, 3 years). However, identification of large groups of these patients is challenging due to several factors: symptoms that can masquerade as other disorders and diseases,² the seeming rarity of these disorders, limited specialty center locations, and the evolving diagnostic and classification criteria. This survey was conducted as a collaboration between TMS, with its large patient network, and MCD specialists in preparation for the Year 2010 Working Conference on MCD.²

Two large European registries have provided previous estimates of patient experiences: REMA (Red Española de Mastocitosis), a Spanish network for mastocytosis¹⁰ and AFIRMM (Association Française pour les Initiatives de Recherche sur le Mastocytes et les Mastocytoses), a French mastocytosis organization.¹¹ Although numerous clinical studies and a survey that focused on autism¹² have been published, no previous in-depth survey of US patients with mastocytosis, MCAS, and related MCD has been identified.

TABLE II. Severity and frequency of pain and other symptoms among 420 respondents

Symptom	Severity			
	Any*		Moderate or extreme	
	Total responses, no. (%)	Daily or occasionally, no. (%)†	Total responses, no. (%)	Daily or occasionally, no. (%)‡
Pain				
Stomach	306 (72.9)	275 (89.9)	253 (60.2)	244 (96.4)
Lower abdomen	237 (56.4)	202 (85.2)	194 (46.2)	179 (92.3)
Joint	258 (61.4)	228 (88.4)	193 (46.0)	188 (97.4)
Bone	237 (56.4)	197 (83.1)	190 (45.2)	166 (87.4)
Muscle, nerve, connective tissue	210 (50.0)	185 (88.1)	166 (39.5)	158 (95.2)
Upper abdomen	195 (46.4)	159 (81.5)	151 (36.0)	138 (91.4)
Chest	154 (36.7)	96 (62.3)	96 (22.9)	73 (76.0)
Other				
Fatigue	320 (76.2)	296 (92.5)	262 (62.4)	255 (97.3)
Headache	267 (63.6)	202 (75.7)	216 (51.4)	182 (84.3)
Brain fog and/or cognitive difficulties	281 (66.9)	242 (86.1)	193 (46.0)	184 (95.3)
Lightheadedness/syncope	257 (61.2)	182 (70.8)	185 (44.0)	146 (78.9)
Weakness	225 (53.6)	173 (76.9)	171 (40.7)	149 (87.1)
Anaphylactic shock	175 (41.7)	82 (46.9)	158 (37.6)	80 (50.6)
Anxiety	255 (60.7)	190 (74.5)	156 (37.1)	146 (93.6)
Depression	207 (49.3)	148 (71.5)	121 (28.8)	111 (91.7)
Wheezing or asthma	186 (44.3)	125 (67.2)	111 (26.4)	92 (82.9)
Angioedema	146 (34.8)	83 (56.8)	107 (25.5)	66 (61.7)
High blood pressure episodes	123 (29.3)	93 (75.6)	89 (21.2)	72 (80.9)
Cardiac	120 (28.6)	83 (69.2)	82 (19.5)	66 (80.5)

*Any severity: extreme, moderate, or a little bit.

†The percentage of the total with any severity.

‡The percentage of the total with moderate or extreme severity.

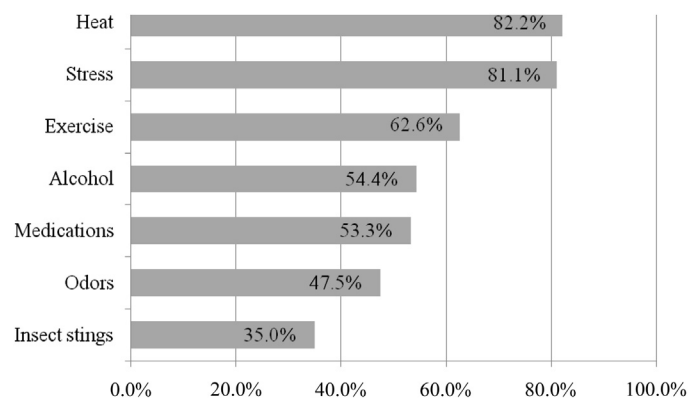


FIGURE 2. The percentage of 366 respondents who selected or listed specific trigger types. Common write-in triggers were various foods (31.1%), cold (13.9%), food additives (9.3%), friction and/or pressure (8.7%), fatigue (6.8%), and chemicals (4.9%). Less common write-in triggers are provided in [Table E6](#).

Thus, these TMS survey results represent the first comprehensive US survey of patients with these disorders.

This survey has several strengths. Key strengths are the 420 valid responders and high survey completion rate. Internet availability allowed participation of patients not treated at specialty centers. The results provide a realistic account of problems and demographics of those who present to medical providers with a possible MCD diagnosis. Also, the survey was not funded by any entity with a commercial or financial profit interest.

Several weaknesses inherent to all population-based surveys without medical professional assistance exist.¹³ Some respondents may have had other diseases, and even some respondents who actually had MCD may have reported symptoms or problems not related to their MCD. People who entered the survey may have tended to be those who were more active in online discussion and support groups, and/or had more severe problems.¹³ Certain responses would have been subject to limitations of patient recall and bias, for example, interpretation of information received from

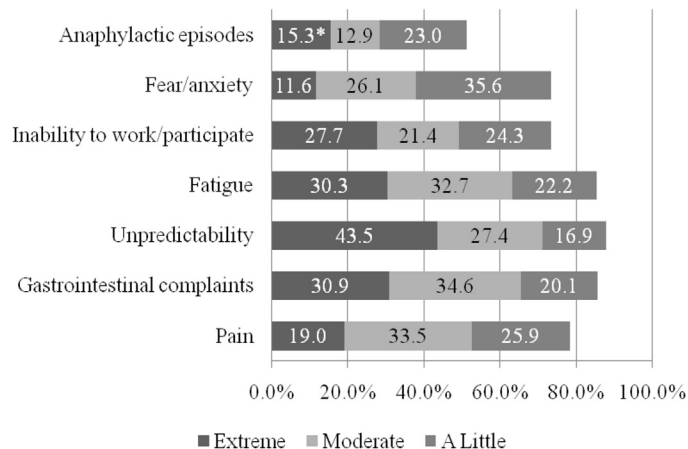


FIGURE 3. The percentages that represent aspects of life with a MCD among 379 respondents selecting extreme, moderate, or a little effect regarding coping. The percentages are not displayed for those who selected “not at all” (4% to 5% did not answer these questions). *All numbers represent percentages.

medical professionals. It is important to note that creation of a medically accurate database, which would have required a review of patient medical records by medical professionals, was beyond the intention and realistic expectations of this survey. A comparison of this survey sample with another sample without MCD would have been ideal; however, choosing such a sample would have been extremely complex and beyond the scope and resources of TMS. Because of these limitations, caution must be used when comparing results of this survey with other studies.^{3,8,10,11,14-19}

Nearly one-third of survey respondents who reported a diagnosis of mastocytosis were determined to have CM without SM; however, only 40% of the adults with CM reported having had a bone marrow biopsy. Even when bone marrow biopsies are performed, the biopsies or associated laboratory studies may be performed incorrectly. Even if they are performed appropriately, mastocytosis can be missed²⁰; accordingly, it is possible that this survey underestimates the percentage of patients with SM.

It is interesting to note that the case-controlled AFIRMM study mentioned above identified similar percentages regarding specific symptoms for patients who experienced any severity (TMS) or any disability (AFIRMM) for the following: fatigue, itching, headache, bone pain, depression, and nausea and/or vomiting.¹¹ In both analyses, these numbers identify all the patients who experienced a given symptom, despite the level of severity or disability. Other related symptoms with similar frequencies, but different query terms, include the following: for TMS (AFIRMM), wheezing and/or asthma (dyspnea and/or bronchoreactivity), stomach pain (epigastric pain), and brain fog and/or cognitive difficulties (memory loss). AFIRMM identified 76% with any disability from muscle and joint pain, cramps, whereas TMS separately queried joint and muscle, nerve, and/or connective tissue pain. In the TMS analysis, yes answers to either or both questions were combined, which yielded 66.7% (280 respondents).

Two symptoms (any severity and/or any disability) with similar patient queries were reported at higher levels to TMS: flush (76.4%, TMS; 52%, AFIRMM) and diarrhea (66.0%, TMS; 35%, AFIRMM). Although the reasons for these differences are unknown, they may relate to different survey methods and/or populations queried. Gastrointestinal symptoms were experienced by 65% of patients with mastocytosis from a large

US clinic.⁸ Various gastrointestinal symptoms of any severity were experienced by 53.8% to 66.0% of TMS survey respondents and required moderate or extreme coping for 65.5%.

Many patients with MCD have more than one condition, for example, mastocytosis with allergy, and coexistence can aggravate symptoms of MCA. Increased awareness of such coexistence may help in the diagnosis and management of these patients. The REMA study in Spain reported that allergy symptoms were suggested in 57% of adult patients with mastocytosis; however, true allergy prevalence (clinical symptoms related to specific IgE) in the Spanish study was actually 23.9%, similar to that of the general Spanish population.¹⁰ A US-based study reported that 31% of 48 adult patients with mastocytosis had a history of allergic diseases or food allergy.¹⁵ A study of 120 German patients with mastocytosis found a history of allergic diseases at levels no higher than the general population (28% in adults).¹⁶

The TMS survey sections for allergies and triggers presented a challenge in that patients may have been unable to differentiate, without testing, between allergies and nonallergic intolerances or triggers and/or provoking factors.^{2,16} Although clinical verification of IgE-mediated allergies was not possible, more than half of the TMS allergy section respondents reported a positive allergy test for at least one of the allergen types queried. Interestingly, high levels of allergy and/or intolerance were found for food and/or beverages (50.3% of respondents) and drugs (58.3%), similar to the AFIRMM survey (61% reporting any disability from food allergy/intolerance and 56% from drug allergy).¹¹ Nearly all respondents noted at least one MCD symptom trigger, and many provoking factors were similar to reports found in the literature.^{3,4,6,9,16,21,22}

Anaphylaxis rates for specific MCD patient populations may be influenced by sex, age, MCD classification, and the presence of skin lesions^{8,10,11,16,18,23} and have been reported at rates up to 49% in adult patients with mastocytosis.¹⁶ In addition to food and drug reactions, reports indicate 20% to 30% of patients with mastocytosis experience insect venom-induced anaphylaxis.^{16,24}

The TMS survey used the term anaphylactic shock along with a severity scale, which, although medically incorrect, may have been interpreted by patients as “anaphylaxis.” Anaphylactic shock of any severity was reported by 175 TMS survey respondents (41.7%). The AFIRMM study identified 44% who

experienced any disability from anaphylactic shock.¹¹ A German study reported that unconsciousness was experienced in 53% of adult patients with mastocytosis and with anaphylaxis.¹⁶ Although “unconsciousness” was not queried in the TMS survey, 109 people (26.0% of respondents) had experienced anaphylactic shock with extreme severity. In addition, 28.2% of participants noted that they were affected either moderately or extremely regarding coping with anaphylactic episodes. Although patients with mastocytosis and related MCD have increased anaphylaxis risk,^{10,16,25} this survey found only slightly more than half of the respondents always carry medical alert jewelry and/or cards or self-injectable epinephrine. Survey responses regarding symptom relief medications were too complex to include in this report. However, the authors note that cytoreductive agents are generally not used to treat indolent SM. Medication recommendations are available and depend on MCD type.^{1,2,9,18,26-29}

The findings of this survey highlight a need for education of physicians in multiple disciplines, improved methods for recognition of patients with potential MCD and clear criteria for diagnosing MCD. Survey results were reported to specialists at the 2010 MCD Working Conference. The conference report includes proposed disease definitions, classifications, and diagnostic criteria.² Patient priorities identified through this survey, and a similar unpublished survey of patients in the European Union also were included.² It is hoped that this TMS survey will help MCD specialists, other physicians, and patients to better understand the experiences and perceptions of those living with mastocytosis, MCAS, and related disorders.

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REFERENCES

- Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37:435-53.
- Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012;157:215-25.
- Alvarez-Twose I, Gonzalez de Olano D, Sanchez-Munoz L, Matito A, Esteban-Lopez MI, Vega A, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *J Allergy Clin Immunol* 2010;125:1269-1278.e2.
- Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 2010;126:1099-1104.e4.
- Sonneck K, Florian S, Mullauer L, Wimazal F, Fodinger M, Sperr WR, et al. Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: monoclonal mast cell activation syndrome. *Int Arch Allergy Immunol* 2007;142:158-64.
- Valent P, Horny HP, Triggiani M, Arock M. Clinical and laboratory parameters of mast cell activation as basis for the formulation of diagnostic criteria. *Int Arch Allergy Immunol* 2011;156:119-27.
- Horan RF, Austen KF. Systemic mastocytosis: retrospective review of a decade's clinical experience at the Brigham and Women's Hospital. *J Invest Dermatol* 1991;96(Suppl):5S-13S; discussion S-4S, 60S-5S.
- Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood* 2009;113:5727-36.
- Hamilton MJ, Hornick JL, Akin C, Castells MC, Greenberger NJ. Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations. *J Allergy Clin Immunol* 2011;128:147-152.e2.
- Gonzalez de Olano D, de la Hoz Caballer B, Nunez Lopez R, Sanchez Munoz L, Cuevas Agustin M, Dieguez MC, et al. Prevalence of allergy and anaphylactic symptoms in 210 adult and pediatric patients with mastocytosis in Spain: a study of the Spanish network on mastocytosis (REMA). *Clin Exp Allergy* 2007;37:1547-55.
- Hermine O, Lortholary O, Leventhal PS, Catteau A, Soppelsa F, Baude C, et al. Case-control cohort study of patients' perceptions of disability in mastocytosis. *PLoS One* 2008;3:e2266.
- Theoharides TC. Autism spectrum disorders and mastocytosis. *Int J Immunopathol Pharmacol* 2009;22:859-65.
- Rothman KJ, Greenland S. Precision and validity in epidemiologic studies. *Modern Epidemiology*. 2nd ed. Philadelphia: Raven Publishers; 1998. p. 115-34.
- Muller U, Helbling A, Hunziker T, Wuthrich B, Pecoud A, Gilardi S, et al. Mastocytosis and atopy: a study of 33 patients with urticaria pigmentosa. *Allergy* 1990;45:597-603.
- Brockow K, Akin C, Huber M, Metcalfe DD. Assessment of the extent of cutaneous involvement in children and adults with mastocytosis: relationship to symptomatology, tryptase levels, and bone marrow pathology. *J Am Acad Dermatol* 2003;48:508-16.
- Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008;63:226-32.
- Pardanani A, Lim KH, Lasho TL, Finke CM, McClure RF, Li CY, et al. WHO subvariants of indolent mastocytosis: clinical details and prognostic evaluation in 159 consecutive adults. *Blood* 2010;115:150-1.
- Escribano L, Alvarez-Twose I, Sanchez-Munoz L, Garcia-Montero A, Nunez R, Almeida J, et al. Prognosis in adult indolent systemic mastocytosis: a long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. *J Allergy Clin Immunol* 2009;124:514-21.
- Lantier F, Cohen-Akenine A, Palmerini F, Feger F, Yang Y, Zermati Y, et al. Phenotypic and genotypic characteristics of mastocytosis according to the age of onset. *PLoS One* 2008;3:e1906.
- Butterfield JH, Li CY. Bone marrow biopsies for the diagnosis of systemic mastocytosis: is one biopsy sufficient? *Am J Clin Pathol* 2004;121:264-7.
- Escribano L, Orfao A. Anaphylaxis in mastocytosis. *Anaphylaxis and Hypersensitivity Reactions*. New York: Humana Press; 2011. p. 257-69.
- Akin C, Metcalfe DD. Mastocytosis and mast cell activation syndromes presenting as anaphylaxis. *Anaphylaxis and Hypersensitivity Reactions*. New York: Humana Press; 2011. p. 245-56.
- Sanchez-Munoz L, Alvarez-Twose I, Garcia-Montero AC, Teodosio C, Jara-Acevedo M, Pedreira CE, et al. Evaluation of the WHO criteria for the classification of patients with mastocytosis. *Mod Pathol* 2011;1-12.
- Niedoszytko M, de Monchy J, van Doormaal JJ, Jassem E, Oude Elberink JN. Mastocytosis and insect venom allergy: diagnosis, safety and efficacy of venom immunotherapy. *Allergy* 2009;64:1237-45.
- Simons FE, Arduzzo LR, Biló MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;127:587-593.e1-22.
- Metcalfe DD. Mast cells and mastocytosis. *Blood* 2008;112:946-56.
- Pagano L, Valentini CG, Caira M, Rondoni M, Van Lint MT, Candoni A, et al. Advanced mast cell disease: an Italian hematological multicenter experience. *Int J Hematol* 2008;88:483-8.
- Valent P, Sperr WR, Akin C. How I treat patients with advanced systemic mastocytosis. *Blood* 2010;116:5812-7.
- Escribano L, Akin C, Castells M, Schwartz LB. Current options in the treatment of mast cell mediator-related symptoms in mastocytosis. *Inflamm Allergy Drug Targets* 2006;5:61-77.