Mast Cell Activation

When the Whole Is Greater than the Sum of Its Parts

Dilawar Khokhar, MD, Cem Akin, MD, PhD*

KEYWORDS

• Mast cell activation • MCAS • Mast cell disorder • Mastocytosis
• Idiopathic anaphylaxis • Tryptase • Mast cell mediators

KEY POINTS

- Mast cell activation syndrome (MCAS) is a rare, distinct clinical entity with severe episodic symptoms of mast cell activation associated with elevated mast cell mediators.
- Idiopathic anaphylaxis should be viewed as the prototypical manifestation of MCAS and can be used to establish a framework for evaluation.
- No single sign, symptom, or laboratory test is sufficient for the diagnosis of MCAS.
- Therapy for MCAS is based on avoidance of triggers and antimediator therapy.

INTRODUCTION

Mast cells are important immunomodulatory cells that are located at the junction of the internal and external environment and release a host of mediators that have significant downstream effects.[1,2] When they are dysfunctional, their location and mediator release result in a broad range of symptoms. One entity that highlights this is mast cell activation syndrome (MCAS). MCAS is a heterogeneous and rare disorder with episodic and severe activation of mast cells.[3–9] Because symptoms of mast cell activation (MCA) are nonspecific, it is important to base the diagnosis on the best available clinical and scientific evidence, and not make it one of exclusion. MCAS, much like the mast cell itself, as a whole is greater than the sum of its proposed diagnostic criteria. When each component is considered in isolation, criteria can seem nonspecific, and thus, a broad constellation of symptoms can be attributed to MCAS when they may be due to other disease processes. Nonspecific symptoms can make it challenging for clinicians to correctly identify MCAS and is equally frustrating for patients who may undergo expensive and unnecessary workups or receive ineffective treatment of their symptoms as a result of

Department of Internal Medicine, Division of Allergy and Clinical Immunology, University of Michigan, 24 Frank Lloyd Wright Drive, Lobby H Suite H-2100, Ann Arbor, MI 48106, USA
* Corresponding author.
E-mail address: cemakin@med.umich.edu

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misdiagnosis.[10,11] It is thus essential to develop a systematic approach when considering the diagnosis of MCAS.

THE MAST CELL AND ITS DISORDERS

The mast cell is a granulocytic cell first described by Paul Ehrlich in 1877.[12] Since their discovery, mast cells have been implicated in several physiologic and pathogenic processes. Although they are best known for their role as the effector cells of immediate type hypersensitivity reactions, they play an important role as immunomodulatory cells, releasing a host of proinflammatory as well as anti-inflammatory mediators affecting the interaction of the immune system with the surrounding microenvironment.[12,13] Their location in connective tissue, the gastrointestinal (GI) tract, and the respiratory tract allows them to often be a first responder when there is a change in environment.[12,13] Dysfunction of mast cells thus can manifest across several different organ systems. MCA may occur at the local level (such as in urticaria) or systemically (as is the case in anaphylaxis).[14] There is no specific symptom or afflicted organ system for mast cell dysfunction, so it is important to establish a systematic approach or framework when considering a mast cell disorder (MCD) in a given patient.

MCDs can be thought of as primary, secondary, or idiopathic.[7,9] In primary MCDs, there is an intrinsic defect within the mast cell or its progenitors resulting in pathologic condition (**Table 1**). Because these disorders are due to an intrinsic cell defect, they are typically clonal disorders that are associated with KIT mutation and include conditions such as systemic mastocytosis.[8,15–17] In secondary MCDs, there is a primary disease process, such as immunoglobulin E (IgE)-mediated hypersensitivity, that results in mast cell degranulation (nonclonal MCA).[7,9] Finally, there are idiopathic MCDs whereby no specific mast cell deficiency or systemic disease triggering MCA is identified, but MCA occurs.[7,9] MCAS is a severe form of episodic MCA that may be associated with primary, secondary, or idiopathic MCD.

DEFINING MAST CELL ACTIVATION SYNDROME

Various criteria have been proposed for the diagnosis of MCAS.[4,18] The authors strongly recommend the following criteria, which have been accepted by an international group of experts and is based on best available evidence[3–9]:

1. Episodic and recurrent symptoms of mast cell mediator release affecting 2 or more organ systems
2. Complete resolution of symptoms or decrease in the frequency or severity of symptoms with antimast cell mediator therapy (antihistamines, leukotriene modifiers, and mast cell stabilizer agents)
3. Evidence of an increase in a validated urinary or serum marker of MCA (ideally with reproducible results obtained during more than 1 symptomatic episode)

Table 1
Examples of mast cell disorders

MCD Type	Examples
Primary	Mastocytosis, monoclonal mast cell activation syndrome (MMAS), mast cell sarcoma, mastocytoma
Secondary	IgE-mediated hypersensitivity, physical urticarias, mast cell hyperplasia (owing to systemic disease such as chronic infection or autoimmune disease)
Idiopathic	MCAS, idiopathic anaphylaxis, chronic idiopathic urticaria/angioedema

It is important to remember that such criteria may apply to primary, secondary, or idiopathic MCA, and the workup for primary and secondary causes may be pursued concurrently. There is no single pathognomonic clinical presentation for MCAS, and thus, it is essential that all 3 consensus criteria be fulfilled before the diagnosis of MCAS is established. An important consideration when assessing for idiopathic MCAS is whether the patient meets criteria for idiopathic anaphylaxis. Idiopathic anaphylaxis is defined as anaphylaxis that is not explained by a presumed or proven cause or stimulus.[12] It is considered a distinct clinical entity, but in the authors' point of view, it should be considered a subtype of MCAS that meets the diagnostic criteria for anaphylaxis because the only effector cells of anaphylaxis in humans are mast cells.[3,15,19] Thus, idiopathic MCAS is a broader entity that includes idiopathic anaphylaxis (IA) and may be a more appropriate term for the patients whose episodes may not meet the clinical definition of anaphylaxis, or who may experience idiopathic episodes mixed with episodes owing to particular triggers. This may be difficult to differentiate from patients with chronic urticaria and angioedema who may also experience extracutaneous symptoms, which can be features of both secondary and idiopathic MCA.[3] This is where the paradigm of IA as the archetypal form of MCAS is helpful because patients with anaphylactic features in which the symptoms involving multiple organ systems occur in distinct episodes are more likely to have an underlying MCAS.[3]

MAST CELL MEDIATORS AND CLINICAL MANIFESTATIONS

In order to gain a better understanding of MCA, one must first characterize mast cell mediators as well as their clinical manifestations (**Table 2**). Perhaps the most well-studied mast cell mediator is histamine. Histamine is a biogenic amine compound that was first described by Henry H. Dale and P.P. Laidlaw in 1910.[20] It is predominantly stored in mast cells and in basophil granules.[21] Histamine exerts its effects in the human body via G-coupled protein receptors.[20] It has a multitude of effects, including modulation of local immune responses, itching, the sleep-wake cycle, body temperature, bronchoconstriction, and vasodilation, to name a few.[20] This underscores the importance of mast cells in maintaining homeostasis and is perhaps one of the reasons that disorders of mast cells manifest with such nonspecific symptoms across a host of different organ systems. Despite its central role in the generation of symptoms of MCDs, assessment of histamine in the clinical setting remains of limited utility. This is due to the variability of blood and urine levels because histamine is influenced by several extrinsic factors, including the method by which samples are obtained and stored, as well as diet.[3,22] Elevated urinary histamine metabolites (eg, N-methylhistamine) may support the diagnosis of a MCD,[3,22] especially when associated with other mediator elevations, but age and disease-specific cutoffs in MCAS

Table 2
Common manifestations of mast cell mediator release

System	Symptoms
Skin	Urticaria, angioedema, flushing
GI	Nausea, vomiting, diarrhea, abdominal cramping
Respiratory	Wheezing
Nasal/ocular	Conjunctival injection, pruritus, nasal congestion
Vascular	Hypotension

have not been extensively studied, and a single elevated level should be evaluated in the appropriate clinical context and in the presence of other criteria supporting the diagnosis. Available data on patient perceptions of MCDs suggest that patients perceive significant difficulty with establishing a diagnosis of MCD,[10] 1 factor that likely contributes to this variance in interpretation of mast cell mediator studies.[10] In the authors' clinical experience, isolated elevations in a single mediator are generally insufficient to establish a diagnosis. If elevations in mast cell mediators are identified, patients should be referred to a specialist with experience in diagnosing and treating MCDs because MCA markers may need to be repeated to verify the diagnosis.

Prostaglandin D2 is an eicosanoid synthesized and released by mast cells[23,24] within a few minutes of MCA. It plays an important role in the generation of immune responses, including recruitment of T lymphocytes, eosinophils, and basophils.[25,26] One of its primary clinical effects is bronchial airway constriction, particularly in asthma after contact with aeroallergens.[25,26] Metabolites of prostaglandin D2, including 11-β-prostaglandin F2α, can be measured in the urine.[27] Prostaglandin D2, while primarily released by mast cells, is also found in other immune and nonimmune cell types, including macrophages, T lymphocytes, platelets, and the central nervous system.[25,27] This is important to recognize because elevations in prostaglandin D2 may be due to processes independent of MCA.

Leukotrienes have long been known to play a central role in inflammation and many allergic diseases.[28] Leukotriene C4 (LTC4) is an arachidonic acid derivative that is released by mast cells[22] and undergoes metabolism into leukotriene D4 and then to E4.[29,30] LTC4 has been implicated in several disease states, including asthma, allergic rhino-conjunctivitis, and atopic dermatitis.[29] LTE4 can be detected in the urine and thus can be used as a potential marker of MCA, although the degree of elevation correlating with various MCDs has not been well defined. Patients with predominant respiratory, nasal, or ocular symptoms may have a greater release of leukotrienes and thus represent a target phenotype in MCDs for antileukotriene therapies.

The most specific marker of MCA is tryptase, a serine protease predominantly associated with mast cells.[31–33] Mast cell tryptase can be categorized into 2 major groups, a protryptase (mainly encoded by the α-tryptase gene in TPSAB1 locus), which lacks enzymatic activity, and mature tryptase (predominantly encoded by the β-tryptase gene at the same locus).[33–36] β-Tryptase is the form stored in mast cell granules and is increased after MCA, whereas α-tryptase is a proenzyme that is secreted outside of the cells and thus is the form of tryptase detected in the blood at baseline conditions.[33–35] There is an increase in β-tryptase when mast cell granulation occurs with peak levels occurring at approximately 1 hour and mostly returning to baseline levels by 4 hours.[33–35] A normal tryptase level is typically considered 5 ng/mL or less. A level greater than 11.4 ng/mL is considered elevated by most clinical diagnostic laboratories. An elevated baseline tryptase level can be indicative of increased mast cell burden, and a level of greater than 20 ng/mL is a minor diagnostic criterion for the diagnosis of systemic mastocytosis.[37] A change of 20% of baseline tryptase plus 2 ng/mL is indicative of a MCA episode.[37] Thus, a normal tryptase level at baseline does not exclude MCA. Many patients may have baseline normal tryptase levels that increase acutely with MCA episodes, especially with systemic symptoms, such as hypotension. It is paramount to obtaining more than 1 tryptase level when assessing for MCAS, ideally a baseline level and level drawn shortly after onset of symptoms (preferably 1 hour or less after onset of symptoms).

The biological activities of tryptase include cleaving of extracellular substrates, such as vasoactive intestinal peptide, kininogens, and fibronectin, as well as stimulating the release of various inflammatory mediators, such as interleukin-8 (IL-8).[31–33] It has been

implicated in the upregulation of intercellular adhesion molecule-1 as well as increased messenger RNA expression for IL-1β.[32] In addition, tryptase release from activated mast cells may stimulate secretion from neighboring mast cells.[32] These constellations of findings support tryptase as more than just a marker of MCA, but an enzyme that plays an important role in the immunologic cascade that occurs after mast cell degranulation.

Although tryptase is the most specific marker for MCA, it can be elevated by other processes, including chronic kidney disease, myeloid neoplasms, hypereosinophilic syndromes, and hereditary αhypertryptasemia (HAT).[32,34,38] HAT is important to consider because it represents a pitfall for clinicians in the evaluation of MCAS. It is a recently described condition whereby there is overproduction of α-tryptase owing to copy number variations of the α-tryptase gene encoded at the TPSAB1 locus and is estimated to be present in 6% of the population.[38] The clinical significance of HAT is currently investigated, but mast cells from individuals with HAT do not seem to have a hyperreleasable phenotype. The genetic test for tryptase copy number variation is available clinically (genebygene.com), but may not be covered by insurance.

Historically, another important consideration when evaluating elevated tryptase levels has been laboratory interference.[39] Heterophilic antibodies, such as rheumatoid factor and human antimurine antibodies, have been reported to interfere with immunoassays, such as the tryptase laboratory assay.[39,40] Since the recognition of this phenomenon, commercial tryptase laboratory assays have introduced heterophilic blocking agents to resolve this laboratory interference. This again demonstrates the importance of interpreting laboratory results in the proper clinical context. In the authors' clinical experience, laboratory interference is now an uncommon occurrence, but any suspicious results should be repeated. Providers may need to contact specific laboratories directly to verify if heterophilic blocking agents are used when the tryptase assay is run. It is critical to correctly identify significant tryptase elevation, because bone marrow biopsy may be indicated for evaluation for systemic mastocytosis and other clonal MCDs.[9]

DIFFERENTIAL DIAGNOSIS

The symptoms attributed to MCA, such as flushing, are nonspecific and can be attributed to several different diagnoses, thus leading to a broad differential.[41] Conditions not carrying the typical hallmark symptom of anaphylaxis and those with chronic daily rather than episodic presentation represent a particular challenge for clinicians because it is difficult to ascribe these to MCA with any degree of certainty (**Box 1**).

The differential diagnosis for MCAS can be overwhelming to the point where it may seem any collective of symptoms is attributable to MCAS. In the authors' opinion, it is helpful to view MCAS from the perspective of anaphylaxis as the quintessential presentation. MCAS, like anaphylaxis, should be seen as a severe systemic reaction that is the result of mast cell mediator release. Most cases should have clinical features of anaphylaxis. The authors recognize that this view does not address patients with less severe or localized forms of MCA, and further investigation to categorize these patients is needed.

MANAGEMENT OF MAST CELL ACTIVATION SYNDROME

The cornerstones of MCAS management are avoidance of triggers (exposures that result in direct mast cell degranulation; **Table 3**) and pharmacologic therapies targeting mast cell mediators. A broad array of exposures has been described as direct mast cell triggers.[3,4] One of the most common triggers identified by

Box 1
Selected diagnoses considered in differential diagnosis of mast cell activation syndrome

Dysautonomia, including POTS and vasovagal syncope

Endocrine: Carcinoid syndrome, pheochromocytoma, medullary thyroid tumor, adrenal insufficiency

Skin: Rosacea, benign idiopathic flushing, contact or atopic dermatitis, chronic urticaria, dermatomyositis

Neuropsychiatric: Anxiety or panic attacks, seizure disorder, multiple sclerosis, somatoform disorder, eating disorders

Hereditary α tryptasemia

Hereditary or acquired angioedema

Gastrointestinal: Irritable bowel syndrome, inflammatory bowel disease, cyclic vomiting, peptic ulcer disease, eosinophilic gastrointestinal disorders

Cardiac: Arrythmias, coronary artery disease

Drug adverse effects: Niacin-induced flushing, steroid toxicity, withdrawal of adrenergic medications, exposure to sympathomimetics, anticholinergic toxicity, caffeine effect, alcohol use/withdrawal

Abbreviation: POTS, postural orthostatic tachycardia syndrome.

patients for symptoms is food.[10] IgE-mediated food reactions are known secondary MCDs,[7,9] but there are limited data on the role of histamine-containing foods in MCAS, and to date, there are no trials demonstrating the benefit of low-histamine diets in MCAS.[3]

It is in the context of history and reported triggers that an allergic evaluation may be appropriate to help guide avoidance strategies. Different patients may have different triggers; thus, counseling on avoidance should be individualized.

Because mast cells release a plethora of mediators, several different antimediator therapies have been used for the treatment of MCAS.[14,42] Perhaps the most common therapy used in MCAS is antihistamines.[43] This is likely due to clinical experience with these agents, low cost, and favorable side-effect profile. The most common second-generation H1 blockers include cetirizine/levocetirizine, fexofenadine, and loratadine/desloratadine. The authors prefer second-generation H1 blockers because they are of equal or greater efficacy as first-generation antihistamines, are less sedating, have less anticholinergic properties, and have a longer duration of action. First-generation antihistamines, such as diphenhydramine, may be useful for breakthrough symptoms on an as-needed basis. Special consideration should be given to the H1 blocker Ketotifen, which also functions as a mast cell stabilizer. It has been shown

Table 3
Exposures that have been implicated in direct mast cell degranulation

Venoms	Hymenoptera stings, jellyfish, snakes
Drugs	Narcotics, radiocontrast, aspirin/NSAIDs, muscle relaxants, antibiotics
Temperature	Heat or cold
Mechanical stimuli	Friction, pressure, or tissue trauma (surgery, biopsy, or endoscopy)
Miscellaneous	Alcohol, emotional stress, exercise, infections

to be helpful in steroid-dependent idiopathic anaphylaxis,[12] and in the authors' experience, is often helpful as a step-up therapy in MCAS. Ketotifen is not Food and Drug Administration approved in oral form in the United States, but can be obtained through compounding pharmacies.

H2 blockers, such as ranitidine or famotidine, have been used as adjunctive medications for patients with MCAS.[14,42] Given that H2 receptors are primarily present in the GI tract, H2 blockers may have greater effect for patients with GI-predominant symptoms. They may also help alleviate skin symptoms in conjunction with H1 antihistamines.

Leukotriene antagonists and 5-lipoxygenase inhibitors have also been used as adjunctive medications.[14,42] Available agents in clinical practice include montelukast, zafirlukast, and zileuton. Given the role leukotrienes play in airway inflammation and the generation of bronchospasm, these agents may be of greater benefit in patients with wheezing or respiratory predominant symptoms.

Cromolyn is a mast cell stabilizer that has been used for the treatment of mastocytosis in oral formulation.[14,42] Oral form has poor GI absorption and thus has limited systemic effects. Given that it remains primarily in the GI tract, it may have potential benefit in patients with primary GI symptoms as an adjunctive medication.

Glucocorticoids have been used as therapy for MCDs, including MCAS.[14,42] Their primary role is as a therapy for patients with severe refractory symptoms. There are no controlled trials evaluating the efficacy of steroids in acute treatment of anaphylaxis. Glucocorticoid medications have a significant side-effect profile and many negative long-term effects. Side effects, including flushing, and GI irritation may be confused as symptoms of MCA. They should not be used as a first-line therapy for MCAS, and if used, should be tapered to the lowest dose that controls the patient's symptoms.

Aspirin has been used as a medication for the treatment of MCAS.[44] Aspirin is a cyclooxygenase inhibitor and thus reduces the production of prostaglandins, including PGD2 implicated in MCA pathologic condition. It has been suggested that patients with high urinary prostaglandin metabolite levels may benefit from aspirin therapy the most.[44] The patient's tolerance of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be known before considering treatment because severe allergic or idiosyncratic reactions occur in some patients.

Omalizumab is an anti-IgE monoclonal antibody that is currently approved for treatment of allergic asthma and chronic spontaneous urticaria, but also has been used off-label in cases of MCAS recalcitrant to other medical therapies.[13,14,42] Omalizumab binds to free IgE and reduces the density of IgE receptors on mast cells (FCeR1) and thus may reduce stimuli for mast cell mediator release.[13] In addition to its use for patients with severe recalcitrant disease, it may be helpful in liberating steroid-dependent patients from steroids.

There are no randomized clinical trials to demonstrate which medication regimen is superior for MCAS. Several different approaches may be taken, including combination therapy, with gradual tapering once symptom control has been achieved versus a step-up approach whereby patients are started on 1 or 2 agents with additional agents considered if adequate symptom control is not achieved. Factors that may help select 1 agent over another include patient symptoms and measured mediator levels as previously mentioned. Other considerations include cost, insurance coverage, and patient tolerability. In the authors' experience, most patients require at least a daily H1 blocker.

Cytoreductive and signal transduction inhibitor therapies have been used in primary MCDs, such as mastocytosis.[8,42] These treatment modalities are not well studied in nonclonal MCDs, such as MCAS, and are not usually recommended in such settings.

WHEN TO REFER

No discussion of MCAS would be complete without discussing when referral to a specialist is warranted. In the authors' point of view, the following patients would derive the most benefit for evaluation by a specialist for MCDs, including MCAS:

- Patients diagnosed with idiopathic anaphylaxis
- Patients with systemic or cutaneous mastocytosis
- Patients with *severe episodic* symptoms attributable to mast cell release
- Patients with *episodic* symptoms *responsive to antihistamines*
- Patients with persistently elevated or event related increase in tryptase

In the authors' allergy clinical practice, they have also found many patients with a multitude of nonepisodic symptoms referred for MCAS evaluation. More research is clearly needed to evaluate whether there are nonclassical chronic presentations of MCA disorders. The authors' experience is that typically patients presenting with chronic ongoing symptoms of multiple chemical and environmental intolerances, chronic disabling fatigue, multiple food intolerances with negative allergy testing resulting in failure to thrive and severe nutritional deficiencies, and patients whose symptoms do not improve on antimediator (eg, H1 antihistamine therapy) are not likely to substantially benefit from an allergist referral, because there remains no objective evidence to implicate a central primary MCD in pathogenesis of these conditions. Some of these patients with complex presentations involving multiple chronic organ system symptoms may have secondary or reactive MCA, and some symptoms, such as itching and flushing, may respond to H1 antihistamine therapy, but this is usually not the disabling or a life-threatening component of their presentation. It is therefore important to identify the underlying pathologic condition causing secondary mast cell activation, because focusing solely on MCA may delay the appropriate workup and treatment of the underlying disorder. These patients are best approached through a multidisciplinary effort with the primary care physician playing a central role as a team leader and synthesizing the data from multiple subspecialists.

FUTURE DIRECTIONS

When all 3 consensus criteria are fulfilled, MCAS represents a rare distinct clinical entity. Unfortunately, this does not address patients with less severe and more localized symptoms owing to MCA, and more refined diagnostic criteria are needed for less severe or secondary forms of MCA. This requires not only continued efforts in understanding mast cell biology and signal transduction but also clinical identification of more useful surrogate markers of MCA in addition to those discussed above. Ehlers-Danlos syndrome and postural orthostatic tachycardia syndrome have been clinically reported to occur with MCAS, but concrete epidemiologic and pathophysiologic evidence for mast cell involvement is lacking. Finally, clinical phenotype of HAT needs to be studied in larger cohorts to see if it is indeed a susceptibility factor for MCAS. New drug development using new agents targeting known mast cell mediator or signal transduction pathways should be pursued and may help not only with treatment of MCAS but also with more common allergic disorders in which mast cells are involved.

DISCLOSURE

Dr D. Khokhar has nothing to disclose. Dr C. Akin has consultancy agreements with Blueprint Medicines and Novartis.

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