

Mast cell activation syndrome: Myths and realities

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ABSTRACT

Background: Mast cells (MCs) have been implicated in a spectrum of allergic, immunologic, and infectious inflammatory conditions that involve different organ systems. MC activation can occur through several different surface receptors other than the well known IgE mediated pathway.

Methods: We use two representative case reports from our practice to summarize what is currently known about MCAS disorders (reality) so that the clinician can more easily differentiate these conditions from other complex unexplained conditions that are being associated with MC activation (myth).

Results: Many complex MC-related conditions, such as clonal MC diseases, have been well characterized but other MC-related disorders, such as MC activation syndrome (MCAS) and idiopathic anaphylaxis, still remain poorly defined. The current consensus recommendations for a diagnosis of MCAS require clinical symptoms of anaphylaxis that correlate with elevation of a MC activation biomarker(s), which improves with H1-antihistamines.

Conclusion: Clinical symptoms of MCAS can overlap with other conditions, including neurogenic disorders, e.g., dysautonomia, which necessitate the importance for the clinician to render an accurate diagnosis so that appropriate treatment is provided.

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The role of mast cells (MC) in allergic diseases is well known but, with the advent of improved methods for MC research, including *in vitro* cell lines and advanced immunohistochemical and genomic methodologies, we are now appreciating how much of a role MCs play in many other conditions not previously well recognized. It is a myth to believe that MCs are only involved in IgE mediated conditions, such as allergic rhinitis, asthma, food or drug anaphylaxis, or MC disorders, e.g., cutaneous or systemic mastocytosis. MCs also have a fundamental role in innate and adaptive immune responses relevant to infection, autoimmune disorders (e.g., rheumatoid arthritis, bullous pemphigoid), chronic demyelinating disorders (e.g., multiple sclerosis), parasitism, chronic urticaria with or without angioedema, and certain cancer types by regulating tumor growth.¹

In addition, MCs have other nonimmunologic roles in promoting angiogenesis, tissue remodeling, and wound healing. Thus, MCs can respond to a spectrum of endogenous and exogenous stimuli that can protect or harm its host.¹ The focus of this review concentrated on “disorders associated with mast cell disorders” notably MC activation syndrome (MCAS), a more recently defined

condition, and how it can be differentiated from other MC conditions (e.g., hereditary α tryptasemia [HAT] and clonal MC disorders) as well as differentiating the clinical presentation from neurogenic disorders, e.g., dysautonomia, because clinical symptoms can overlap with these conditions. The cases below illustrate an example of a patient who presented with HAT (reality) and one with dysautonomia (myth), which are clinical evaluations being increasingly encountered by the allergist.

CASE 1: REALITY

A 61-year-old woman presented with a history of anaphylaxis to Ceclor (Eli Lilly and Company, Indianapolis, USA). However, over the past 20 years, she endorsed having recurrent episodes of hives, flushing, heart palpitations, diarrhea, dizziness, and hypotension unrelated to a specific cause that were responsive to H1- and H2-antihistamines. A previous workup included a serum tryptase evaluation, which was elevated, at 25 $\mu\text{g/L}$ (reference range, 2.2–13.2 $\mu\text{g/L}$). Results of a bone-marrow biopsy showed that MCs comprised 2% of the entire bone marrow cellularity, with rare spindle-shaped cells and no clustering. Staining for *c-KIT* (receptor tyrosine kinase) mutation was negative, and CD25 staining comprised < 5% of bone marrow cellularity, without atypical features of spindling or clustering. A colonoscopy with a biopsy specimen stained for CD117 revealed > 60 MC/hpf.

Based on the patient's clinical symptoms, exclusion of other causes of anaphylaxis, including α -gal hypersensitivity and the presence of CD25 staining on bone marrow biopsy specimens, a tentative diagnosis of atypical Systemic Mastocytosis (SM) was made. However, the patient continued to experience intermittent symptoms, despite

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aggressive treatment with H1-, H2-, and leukotriene antagonists, and MC stabilizing agents, such as cromolyn sodium and ketotifen, especially in response to nonspecific environmental exposures. A recent genetic test to assess for HAT revealed extra allelic α -tryptase copies at Tryptase Alpha/Beta 1 (*TSPAB1*), which confirmed this diagnosis. Although treatment was not modified based on the results of this test, the patient was reassured with having a definitive diagnosis that explained her condition.

CASE 2: MYTH

A 38-year-old woman with a history of Ehlers-Danlos type 3 (EDS3) syndrome, postural orthostatic tachycardia syndrome (POTS) confirmed by a tilt-table test (TILT) test and multiple drug intolerances presented for evaluation of MCAS because she had been experiencing increased symptoms of chronic flushing, palpitations, migraines, nasal congestion with postnasal drainage, and alternating diarrhea with constipation. Results of a previous gastrointestinal (GI) workup, including an esophagoduodenoscopy and colonoscopy, which included negative staining for MCs, were normal. Biomarkers to assess for MC activation revealed a normal baseline serum tryptase level and tryptase level within 3 hours of an acute flare-up of symptoms as well as normal 24-hour urine tests for N-methylhistamine and prostaglandin (PG) F₂ α . Results of a 24-hour urine test for 5-Hydroxyindoleacetic acid (5-HIAA) and the serum chromogranin A level were negative, which made a neuroendocrine tumor less likely. Serologic testing revealed that the patient had a low total IgE level and negative specific IgE (sIgE) to aeroallergens. Treatment with H1- and H2-antagonists for 4 weeks did not significantly improve her clinical symptoms. The patient was subsequently diagnosed with dysautonomia and treated with a low-dose β -blocker (propranolol 10 mg twice a day), and hydration with electrolytes, and recommended a fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet and to start dicyclomine 10 mg three times a day in addition to starting combination fluticasone and azelastine nasal sprays for her nonallergic rhinitis. She returned 6 weeks later and endorsed significant improvement in her flushing, palpitations, migraines, GI symptoms, and nonallergic rhinitis symptoms.

IMMUNOLOGY OF MC ACTIVATION

Allergists are most familiar with the classic IgE-mediated reactions that involve MCs and basophils, in which initial contact with allergen results in antigen processing and presentation to B lymphocytes that differentiate to plasma cells producing sIgE antibodies to the antigenic determinants of the sensitizing allergen that bind to high affinity high affinity IgE receptor (Fc ϵ RI). On reexposure to the relevant antigenic determinant, there is cross-linking of Fc ϵ RI-bound sIgE antibodies, which leads to cell

activation and release of bioactive mediators that can lead to symptoms of allergy and anaphylaxis.

However, in reality, MCs are much more complex because they express a number of other surface receptors, including protease activated receptor-2, cysteinyl leukotriene receptors (CysLT1R/2R), low affinity receptor for IgE (Fc ϵ RII), *c-KIT* receptor, Mas-related G coupled receptor X2 (MRGPRX2), complement receptors (CR3, CR4), anaphylatoxin receptors (CR3a, CR5a), prostaglandin D₂ receptor 2, neuropeptide receptors, and sialic acid-binding immunoglobulinlike lectin-8. For example, endogenous peptides (*e.g.*, β -defensins, cathelicidin antimicrobial peptide (LL-37), substance P, vasoactive intestinal peptide (VIP), cortistatin, somatostatin) can activate the MRGPRX2 G protein-coupled receptor, which leads to a relatively smaller amount of calcium influx, secretion of small granules, which results in a rapid and transient clinical allergic reaction. Medications, including neuromuscular binding agents, fluoroquinolones, and vancomycin, can also activate either or both the Fc ϵ RI and MRGPRX2 receptors. Stem cell factor can activate the *c-KIT* receptor, which can activate the Fc ϵ RI receptor and inhibit MRGPRX2, whereas both *c-KIT* and the experimental tripeptide, tachykinin receptor 1 (NK1) receptor antagonist Gln-D-Trp(Formyl)-Phe benzyl ester (QWF) can also inhibit MRGPRX2.² Finally, MCs may be activated *via* toll-like receptors by lipopolysaccharides, the pathogen-associated molecular pattern for Gram-negative bacteria, and peptidoglycan, the pathogen-associated molecular pattern for Gram-positive bacteria, which leads to the release of inflammatory cytokines (Fig. 1).³

DIFFERENTIAL DIAGNOSIS

Disorders associated with MC activation includes MCAS, idiopathic anaphylaxis, HAT, and clonal MC disorders. The clinical spectrum of clonal MC disorders is summarized in Fig. 2. Patients may present with milder prediagnostic SM, primarily manifesting as cutaneous symptoms in the presence of increased MC mediators, followed by indolent SM and smoldering SM, in which they experience multiorgan skin, cardiovascular, GI, and neurologic symptoms. Patients with aggressive SM experience episodes of spontaneous anaphylaxis or secondary to drugs, bee stings, or foods with hypotension in conjunction with bone pain, osteopenia or osteoporosis, and constitutional symptoms. Less frequently occurring is SM associated with hematologic malignancy, followed by the much rarer condition, MC leukemia. These later conditions are associated with prominent organopathy and disease burden, and require aggressive medical management with chemotherapy and, for MC leukemia, bone marrow transplantation.⁴ The World Health Organization classification of mastocytosis provides an in-depth overview of clonal MC disorders, which is beyond the scope of this review.⁵ Other conditions that may manifest with many similar symptoms as SM, such

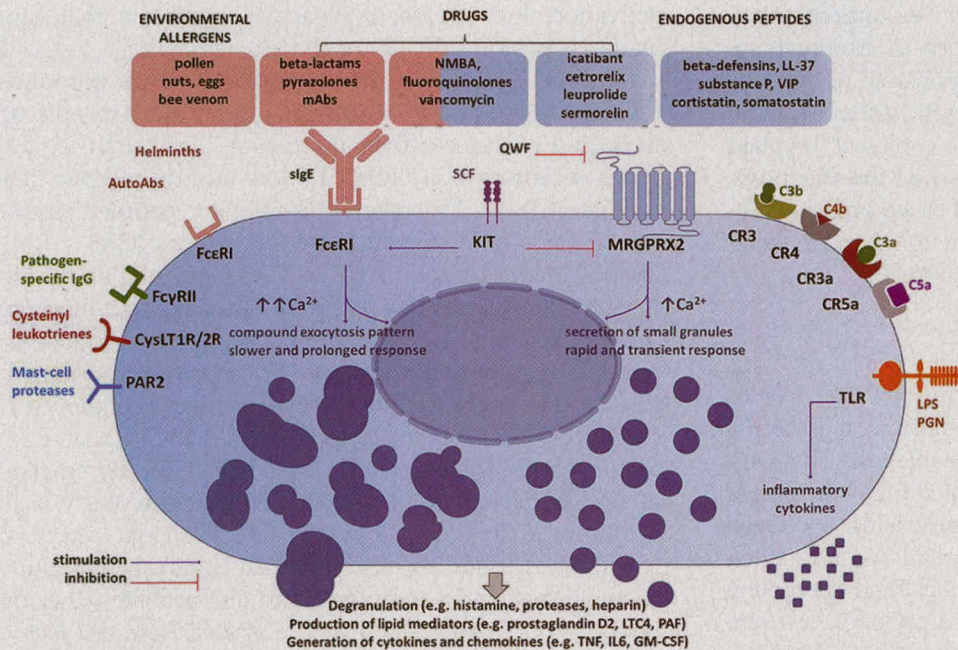


Figure 1. Main receptor systems and examples of ligands involved in mast cell activation (from Ref. 3).

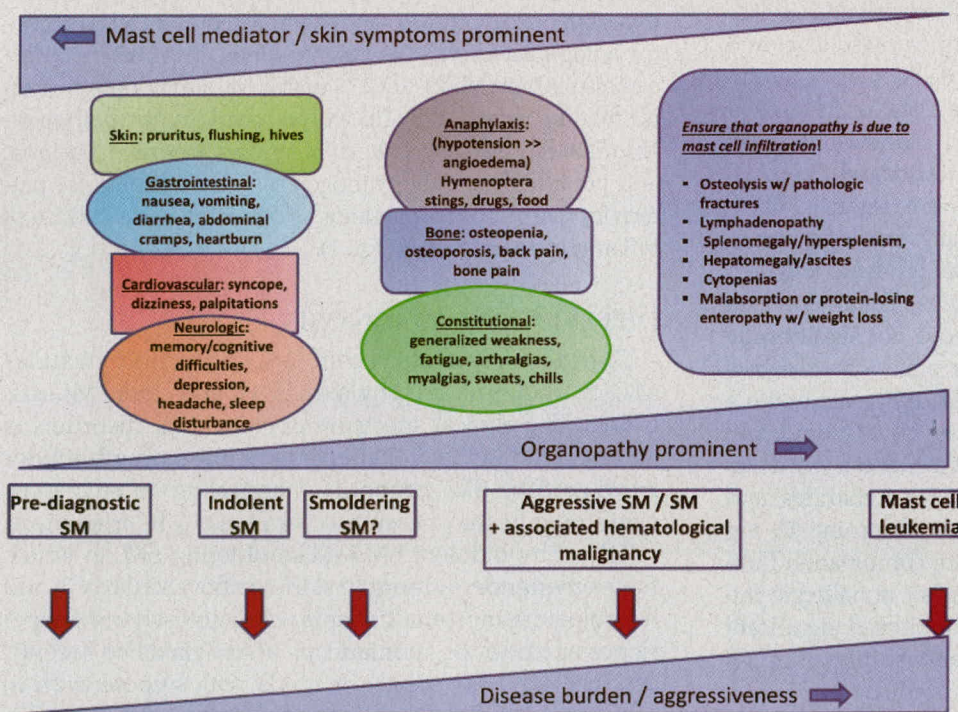


Figure 2. The spectrum of clonal mast cell disorders (from Ref. 6).

as carcinoid syndrome, other neuroendocrine tumors, idiopathic anaphylaxis, HAT, MCAS, and α -gal anaphylaxis, should be excluded. Classification, diagnosis and treatment of MCAS disorders and mimickers are summarized in Table 1.

MCAS

Allergists are currently seeing a surge of patients who present with EDS3, postural POTS, and other

dysautonomic symptoms for further evaluation of MCAS, as seen in case 2. Therefore, it is essential to perform a thorough workup to rule out an MC disorder because these patients exhibit overlapping symptoms with MC disorders. A diagnosis of MCAS requires three criteria: (1) spontaneous episodic signs and symptoms of systemic anaphylaxis that affect at least two organ systems, which results from secreted MC mediators; (2) symptoms that occur in association

with elevation of MC products (e.g., tryptase in blood, N-methylhistamine, PGD₂ and PGF₂ α , and LTE₄ in urine); and (3) improvement of symptoms with medications that block binding of MC products to receptors or their production (e.g., antihistamines, leukotriene-modifying receptor antagonists, cromolyn sodium, ketotifen, omalizumab).⁶ Patients with MCAS can present clinically with cardiovascular (e.g., hypotension, tachycardia, syncope, near syncope), dermatologic (e.g., urticaria; angioedema, particularly of the eyelids, lips, and tongue; pruritus; and flushing), respiratory (e.g., wheezing, shortness of breath, inspiratory stridor), GI (e.g., abdominal pain, diarrhea, nausea, and vomiting), and neurologic (headache, brain fog, and neuropathic leg or arm pain) symptoms.⁶

Involvement of two or more of these organ systems during acute recurrent clinical episodes, also consistent with a diagnosis of systemic anaphylaxis, increases the likelihood of MCAS as a potential diagnosis. Symptoms should be associated with acute increases in MC mediators on two or more occasions to confirm a diagnosis of MCAS. Sometimes the baseline serum tryptase is normal but can increase during an acute episode but requires collection of blood within 1–4 hours after onset because tryptase levels tend to decrease after this time point and any acute increase could be missed. In general, the serum tryptase level is considered the most precise parameter for demonstration and documentation of MCAS, with a consensus proposal of acute serum tryptase levels > 20% of baseline plus 2 ng/mL. For patients who fulfill these criteria, peripheral blood and/or bone marrow biopsy specimens should be obtained to check for the gain of a function *c-KIT* mutation to rule out a clonal MC disease as well as a buccal swab to assess for the Tryptase Alpha/Beta 1 (*TPSAB1*) gene polymorphism associated with HAT.⁶ If negative, then the diagnosis would be considered MCAS, without a known mutation.

Patients who seek evaluation for MCAS often present with a variety of nonspecific and/or atypical symptoms, including fatigue, fibromyalgia-like pain, chronically ill appearance, chronic low back pain, edema, rashes, tinnitus, adenopathy, prostatitis, headache, mood disturbances, anxiety, posttraumatic stress disorder, weight change, hypothyroidism, hyperthyroidism, polycythemia, anemia, abnormal electrolytes, increased or decreased immunoglobulin isotype levels, multiple psychiatric and neurologic disorders, abdominal pain, bloating, distension, diarrhea, and constipation.^{6,7} Reported triggers or potentiating factors for MCAS include hot water, alcohol, drugs, stress, exercise, hormonal fluctuations, infection, and physical stimuli, including pressure and friction.⁶ In addition, there are several disorders that have been associated with MCAS with little-to-no

scientific basis other than clinical associations, including connective tissue disorders (e.g., EDS3), postural POTS, sclerosing mediastinitis, autoimmune disorders, hematologic nonmalignant disorders, solid organ tumors, psychiatric disorders (e.g., depression, anxiety), attention-deficit/hyperactivity disorder, schizophrenia, irritable bowel syndrome, inflammatory bowel disease, gastroesophageal reflux disease, celiac disease and nonceliac gluten intolerance, multiple chemical sensitivity syndrome, endometriosis, polycystic ovarian syndrome, migraine headaches, neurogenic pain syndrome, and restless leg syndrome.⁶

To complicate matters further, there is an overlap with MCAS symptoms and psychiatric conditions, including anxiety, depression, somatoform, and conversion disorders. The increasing recognition of MCAS by psychiatrists and neurologists has resulted in referrals to allergists for evaluation of MCAS. The inappropriate association of these disorders with an MCAS diagnosis has resulted in unorthodox and potentially harmful and inappropriate therapies (e.g., chemotherapeutic agents, tyrosine kinase inhibitors). However, these symptoms and triggers can commonly occur in patients without MCAS, which makes confirming an accurate diagnosis of MCAS more challenging. In fact, physicians and lay persons have broadened the clinical criteria for MCAS to include these symptoms and have also used nonvalidated laboratory tests to support a diagnosis of MCAS. This causes significant confusion for both patients and physicians, which results in misconceptions about the correct diagnosis of MCAS.⁸

HAT

HAT, as illustrated in the case report, is an autosomal dominant disorder caused by a genetic defect that involves one or more extra copies of the α -tryptase gene encoded by Tryptase Alpha/Beta 1 (*TPSAB1*).⁹ It results in overexpression of α -tryptase and may be associated with increased numbers of MCs in bone marrow biopsy specimens, however, not sufficient to satisfy a diagnosis of SM. This condition leads to formation of $\alpha\beta$ -tryptase heterotetramers, which is postulated to contribute to some of the clinical features seen in this condition.¹⁰ The diagnosis of this condition is sometimes overlooked because some patients present with a clinical phenotype consistent with dysautonomia manifesting symptoms of POTS, flushing, GI hypo- or hypermotility, joint hyperextensibility with arthritis, vibratory urticaria, irritable bowel syndrome, or retained primary dentition, in addition to allergic or nonallergic disorders that affect the cutaneous, respiratory, or cardiovascular systems.⁶ In cases of α tryptasemia, a serum tryptase as low as 8.8 μ g/L can be sufficient to establish the diagnosis.

DYSAUTONOMIA

As mentioned, the diagnosis of MCAS can be confounded by the presences of dysautonomia symptoms. There is no standard definition of dysautonomia, which can add to the confusion. Classically, POTS is thought to be due to autonomic dysfunction, and a proposed diagnostic criterion is reproducible orthostatic tachycardia (heart rate rise of ≥ 30 beats/min in patients ages > 19 years and of ≥ 40 beats/min in those ages ≤ 19 years), with symptoms of orthostatic intolerance.¹¹ Patients with POTS can also present with overlapping Ehlers Danlos syndrome type 3, most commonly the hypermobile type, which is a clinical diagnosis. Although symptoms for POTS, EDS type 3, and MCAS may overlap, a diagnosis of one does not mean the presence of the others.¹² For dysautonomia symptoms, low doses of a short-acting β -blockers (e.g., propranolol) can be trialed to reduce headaches, palpitations, and flushing. Clinicians should be cautious when introducing β -blockers because many of these patients have low blood pressure, which can cause dizziness and orthostasis; aggressive hydration with electrolytes is frequently required before initiating. In our experience, there is a significant portion of patients who do tolerate low-dose β -blockers and have benefit in terms of clinically improved symptoms.

DIAGNOSIS OF SYSTEMIC ANAPHYLAXIS

The diagnosis of systemic anaphylaxis is typically made based on clinical criteria and is graded based on the severity, with vascular collapse secondary to hypotension being the most severe reaction. However, as discussed above, overlapping dysautonomia can sometimes be confused with systemic anaphylaxis by physicians and patients. Therefore, it is essential to have reliable biomarkers to differentiate MCAS and other MC disorders from this neurogenic presentation. A serum tryptase test has inherent limitations due to its short half-life and decreased sensitivity. Sometimes normal serum tryptase levels increase above baseline levels during a MCAS flare but still do not increase above the abnormal laboratory range for serum tryptase (< 10 to 11.4 ng/mL, depending on the laboratory). For this reason, the formula, serum acute total tryptase $> (1.2 \times \text{serum baseline tryptase} + 2)$, which calculates a significant increase in serum tryptase from baseline in a patient suspected of having systemic anaphylaxis has been proposed. This test has high specificity ($> 90\%$), whereas sensitivity varies with the time of collection, clinical severity, and trigger.

However, neither serum baseline tryptase or serum acute total tryptase tests by themselves have sufficient sensitivity to assess an MC activation event, regardless of whether it is increased or within the normal range.⁶

The test sensitivity increases with clinical severity, which primarily correlates with hypotension. The optimal time to collect a baseline serum tryptase is either before the event or at least 24 hours after all signs and symptoms have resolved, whereas the optimal time to collect an acute serum tryptase sample based on experimental insect sting-triggered anaphylaxis is 30 to 120 minutes after the onset of symptoms because sensitivity diminishes outside of this range.

TREATMENT OF MCAS

Management of MC-related conditions is aimed toward reducing a patient's morbidity and improving his or her quality of life. Acute treatment of MCAS episodes will vary, depending on clinical symptoms and severity but in severe situations may require epinephrine, supine positioning, bronchodilators, and hydration (oral and intravenous). Preventive treatment may include H1- and H2-receptor antagonists, cromolyn sodium (oral formulation), doxepin, aspirin, corticosteroids, omalizumab, cysteinyl leukotrienes, cyproheptadine, and ketotifen.^{6,13} Often patients present to the allergist after seeing integrative medicine physicians and may be on various diets, including low histamine or FODMAP diets, herbal therapies, and/or other supplements, which have not been shown to be beneficial in the treatment of MCAS or other MC disorders. However, there is literature with regard to the effect of herbal remedies¹⁴ and restrictive diets on MCs; which clinicians should be knowledgeable so they can have an intelligent interactive discussion with the patient rather than immediately dismissing his or her clinical effects as scientifically invalid. These patients often have to be reeducated about the true cause of their underlying condition(s) and the most appropriate treatment options.

Treatment of patients with overlapping MCAS and dysautonomia should be addressed concomitantly. Once a diagnosis of MCAS has been confirmed, the patients should be treated with maximum H1-antihistamine, H2-antihistamine, leukotriene-modifying agents similar to chronic urticaria step 2 therapy.¹⁵ If patients have a high $\text{PGF2}\alpha$, then treatment with low-dose aspirin therapy should be considered. For patients with MCAS and with chronic GI symptoms, an esophago-duodenoscopy with biopsies and staining for MCs and eosinophils should be performed to exclude MC enterocolitis and eosinophilic GI disorders, although the cut point for increased MCs in different regions of the GI tract is still poorly elucidated. If MC counts are present in high numbers (i.e., > 25 MC/hpf), treatment with oral cromolyn sodium should be started, and, if eosinophils are increased, then treatment with a proton-pump inhibitor without or with a swallowed inhaled corticosteroid may be effective at alleviating symptoms and

Table 1 Classification of MC disorders and mimickers

	Symptoms	Diagnosis	Treatment
MCAS	Cardiovascular (<i>e.g.</i> , hypotension, tachycardia, syncope, near-syncope), dermatologic (<i>e.g.</i> , urticaria; angioedema, particularly of the eyelids, lips, and tongue; pruritus; and flushing), respiratory (<i>e.g.</i> wheezing, shortness of breath, inspiratory stridor), GI (<i>e.g.</i> , abdominal pain, diarrhea, nausea, and vomiting), and neurologic (headache, brain fog, and neuropathic leg or arm pain)	Baseline serum tryptase and, if normal, repeat during an acute event within 3–4 hr; N-methylhistamine, PG D211b-PGF2a and LTE4 in urine	H1- and H2-receptor antagonists, cromolyn sodium (oral formulation), doxepin, aspirin, corticosteroids, omalizumab, cysteinyl leukotrienes, cyproheptadine, and ketotifen
Hereditary α tryptasemia	Similar to MCAS	Genetic testing for extra allelic α -tryptase copies at <i>TSPAB1</i>	Symptomatically similar to MCAS
Dysautonomia	POTS, palpitations, dizziness, orthostasis, migraine, flushing, gastrointestinal hypo- or hypermotility, joint hyperextensibility with arthritis, easy bruising, skin laxity, irritable bowel syndrome; more often nonallergic	tilt-table test, clinical signs of EDS3, exclusion of other GI disorders, including MC enterocolitis, exercise ergometry test to assess for cholinergic urticaria if the patient's history suggests	Consider low-dose β -blocker, which can help flushing, migraines, palpitations, cholinergic urticaria; physical therapy for EDS3; hydration with electrolytes and midodrine for POTS; FODMAP diet and dicyclomine for IBS; treat other symptoms/associated disorders as appropriate
Systemic anaphylaxis	Similar to MCAS; impending doom	Tryptase within 3–4 hr of the episode	Avoidance; epinephrine

MC = Mast cell; MCAS = MC activation syndrome; GI = gastrointestinal; PG = prostaglandin; LTE4 = Leukotriene E4; TSPAB1 = Tryptase Alpha/Beta 1; POTS = postural orthostatic tachycardia syndrome; EDS3 = Ehlers-Danlos type 3; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS = irritable bowel syndrome.

confirming the functional relevance of these increased tissue cell counts.

Many of these patients have upper respiratory symptoms triggered by odorants and irritants or weather and/or temperature changes, which can activate transient receptor potential (TRP) channels and cause innervation of nociceptive nerve fibers and stimulation of the parasympathetic nervous system, consistent with nonallergic rhinitis.¹⁶ Treatment with topical intranasal antihistamines (*i.e.*, azelastine, olopatadine) with or without a nasal corticosteroid is helpful in attenuating these symptoms. Lower respiratory symptoms should be assessed with pre- and postbronchodilator spirometry, followed by methacholine challenge if normal and an exhaled nitric oxide test if available to

diagnose or exclude asthma. If the testing result for asthma is negative, then other causes for lower respiratory symptoms, including vocal cord dysfunction, should be assessed. Patients with hypermobility should be evaluated to determine if they fulfill the criteria of EDS3, and, if appropriate, then referred to a geneticist for confirmation as well as physical therapy, which has been demonstrated to reduce pain and prevent musculoskeletal injuries in these patients.

Some patients with dysautonomia may have a condition termed "sympathomimetic syndrome," which is also a mimicker of MCAS.¹⁷ Many of these patients present with recurrent abdominal distension inappropriately diagnosed as angioedema. This syndrome, although still theoretical, is believed to involve

increased sympathetic activity that leads to increased vascular resistance, orthostatic tachycardia, and increased release of norepinephrine and neuropeptide Y.¹⁸ This, in turn, stimulates the MC to secrete bioactive mediators, which causes vasodilation and flushing. In a positive feedback loop, vasodilation then increases sympathetic activity, which cannot counteract the overactive parasympathetic response. In fact, patients with this condition often feel they are having impending doom and self-treat with epinephrine, which leads to symptom improvement. Consistent with this observation, treatment of this defective adrenergic response to vasodilation has been shown to be clinically responsive to sympathomimetic amines.¹⁸

CONCLUSION

MCAS, with or without a genetic mutation of the tryptase gene, is frequently responsive to conventional treatment with medications that block histamine and leukotriene receptors and/or stabilize MC membranes. However, often, patients with dysautonomia present with symptoms that mimic or overlap with MCAS, which makes the diagnosis and management of this condition more challenging. A careful history and categorization of clinical symptoms into MC versus dysautonomia conditions is helpful in determining the best treatment approaches for these patients. Unfortunately, these conditions are still treated symptomatically which necessitates the need for further investigation of relevant neurogenic and immunopathogenic pathways for which targeted precision treatments can be developed.

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