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Mast Cell Activation Syndrome: Proposed Diagnostic Criteria:

Towards a global classification for mast cell disorders

Cem Akin, M.D., Ph.D.,
University of Michigan, Department of Internal Medicine, Division of Allergy and Immunology, Ann Arbor, MI

Peter Valent, M.D., and
Department of Internal Medicine I, Division of Hematology & Hemostaseology Medical University of Vienna and Ludwig Boltzmann Cluster Oncology Vienna, Austria

Dean D. Metcalfe, M.D.
Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Abstract

The term “mast cell activation syndrome (MCAS)” is finding increasing use as a diagnosis for individuals who present with signs and symptoms involving the dermis, gastrointestinal track and cardiovascular system; frequently accompanied by neurologic complaints. Such patients often have undergone multiple extensive medical evaluations by different physicians in varied disciplines without a definitive medical diagnosis until the diagnosis of “MCAS” is applied. However, “MCAS” as a distinct clinical entity has not been generally accepted nor do there exist definitive criteria for diagnosis. Based on current understanding of this disease “syndrome” and on what we do know about mast cell activation and resulting pathology, we will explore and propose criteria for its diagnosis. The proposed criteria will be discussed in the context of other disorders involving mast cells or with similar presentations; and as a basis for further scientific study and validation.

Keywords

Mast cells; tryptase; histamine; mastocytosis; allergy; anaphylaxis; urticaria

Introduction

The last several years have witnessed an increasing use of the term “mast cell activation syndrome (MCAS)” as a diagnosis for individuals who present with signs and symptoms from flushing to hives, abdominal pain to diarrhea, and paresthesias to cognitive dysfunction (See Table E1 in the Online Repository for an example of what is available to the lay public) (1); and where an extensive medical evaluation has failed to identify an etiology. Although “MCAS” as a distinct clinical entity has not been yet recognized nor defined by definitive criteria for diagnosis, there have been scientific publications on the subject, even relating to a possible genetic basis of a “mast cell mediator syndrome” (2). This article will explore the evolution of the application of the term “MCAS” and propose criteria for its diagnosis in the

Corresponding author: Dean D. Metcalfe, M.D., NIH/NIAID/LAD, Building 10/11C207, 10 Center Drive, MSC 1881, Bethesda, MD 20892-1881, 301-496-2165, 301-480-8384 (facsimile), dmetcalfe@niaid.nih.gov.
Currently at Brigham and Women’s Hospital, Department of Medicine, Division of Rheumatology, Allergy and Immunology, Boston, MA.

context of other disorders involving mast cells or with similar presentations; and as a basis for further scientific study and validation

Historical Perspective

In the late 1980's, the existence of "mast cell activation disorders" apparently associated with sudden synchronous mediator release in the absence of evidence of mast cell proliferation began to be discussed in the literature (3). The possibility of such disorders which would have as their basis activated mast cells was considered at a consensus conference to classify variants of systemic mastocytosis. To quote: "There also may be unknown diseases of mast cell activation, in which mast cells either activate at a lower threshold of stimulation, or perhaps resist the usual stimuli to degranulate. The explanation for why some patients would have unexplained flushing or anaphylaxis would then be an abnormal sensitivity of their mast cells to activation" (4), rather than, for example, an increased sensitivity to histamine (5). In the same conference it was suggested that such "systemic mastocyte activation" could be documented biochemically (6). The possibility of such a syndrome would explain signs and symptoms that appeared to suggest a patient has a mast cell proliferative disorder, but where diagnostic criteria for this disease are not met (7).

In the "diagnosis" of "MCAS", patients with such signs and symptoms as flushing, itching, unexplained systemic hypotension, unexplained gastrointestinal disturbances, and unexplained fluctuations in blood pressure (see Table E1 in the Online Repository), usually are first evaluated by an internist, pediatrician or family practitioner, where common causes of such symptoms are eliminated. The patient may then be referred for an evaluation to determine if there is an allergic basis for the presentation. If this work up is negative, it is then logical to consider the patient might have an unrecognized mast cell proliferative disorder (7). If an evaluation for systemic mastocytosis is negative, one possibility to consider is that the patient has a mast cell based disease, but where the mast cell population is not increased in number as would be seen in a mast cell proliferative disorder. Rather the mast cell population is hyperresponsive.

Proof of the concept of the possibility of hyperactive mast cells contributing to disease states is supported by accumulation of data surrounding the acceptance of the designation monoclonal mast cell activation syndrome (MMAS) by a consensus conference to describe patients who experience unprovoked episodes of anaphylaxis; and have met one or two minor diagnostic criteria for mastocytosis but lack the full expression of the phenotype (three minor or one major and one minor criteria (8). The recognition of the MMAS followed reports that patients with mastocytosis have a much higher than expected accumulative prevalence of idiopathic hypotension, reminiscent of idiopathic anaphylaxis (9). This led investigators to examine patients diagnosed with idiopathic anaphylaxis to determine if some individuals within this group may have had minor criteria for mastocytosis or occult mastocytosis. This indeed turned out to be the case (10). The hypothesis was further strengthened by experimental data that demonstrated that a common adaptor molecule, termed NTAL (LAT 2) could be phosphorylated at rest by KIT bearing the common D816V mutation observed in mastocytosis (11). The hyperphosphorylation of NTAL then contributed to enhanced IgE mediated mast cell activation.

Based on these findings and other data, this mastocytosis consensus conference discussed and accepted the concept of a MMAS (8). The ability to diagnose this disorder was supported by a later report (12). More recent studies documenting that patients with anaphylaxis associated with insect stings have mastocytosis or a monoclonal mast cell population underlying increased sensitivity for anaphylaxis further substantiated the concept (13, 14, 15).

Mast Cells and Mediators

Mast cells are derived from hematopoietic stem cells and undergo terminal differentiation in tissues (16). They are found concentrated in locations such as mucosal and endothelial surfaces where tissues interface with the external environment. This is consistent with the current understanding of mast cells as sentinels of innate and adaptive immune systems. While the exact role of mast cells in maintaining the healthy homeostatic state is yet to be understood, mast cells most often come to clinical attention due to their involvement in allergic diseases.

Stem cell factor is the major cytokine involved in mast cell growth and differentiation. SCF can also enhance IgE mediated mast cell degranulation and act as a chemotactic factor (16). SCF acts through KIT, a transmembrane receptor encoded by the proto-oncogene *c-Kit* which has intrinsic tyrosine kinase activity. KIT is activated when it is cross-linked by SCF. Activation of KIT has also been shown to enhance IgE mediated mast cell activation. The D816V point mutation results in constitutive activation of the tyrosine kinase domain of KIT and leads to SCF-independent autophosphorylation of the molecule.

Mast cells are thus activated by both IgE-dependent and IgE-independent mechanisms (see Table E2 in the Online Repository). Regardless of the mechanism, activation of mast cells results in 1) degranulation with resulting release of preformed mediators stored in granules including histamine, heparin, proteases and cytokines such as TNF-α, 2) de novo synthesis of arachidonic acid metabolites (most notably PGD2 and LTC4) from membrane lipids, and 3) synthesis and secretion of cytokines and chemokines (16).

Classification of Diseases Associated with Mast Cell Proliferation/ Activation

Mast cells play a critical role in the genesis or perpetuation of a number of clinical diseases ranging from those associated with an intrinsic or primary defect in mast cells such as occurs in mastocytosis; to diseases where mast cells are recruited through a non-mast cell dependent, extrinsic mechanism, resulting in a disease associated with “secondary” mast cell activation (Table I).

Diseases associated with primary mast cell activation

Currently, there are two well characterized acquired molecular defects resulting in mast cell proliferation: a point mutation (D816V) in *c-Kit* associated with mastocytosis (17); and a translocation involving PDGFRA (FIP1L1-PDGFRA) (18) associated with chronic eosinophilic leukemia with increased mast cells. The latter molecular defect results in a disease primarily manifested by symptoms attributable to eosinophilic proliferation.

Patients with systemic mastocytosis often have episodic symptoms of mast cell activation, such as flushing, lightheadedness, and gastrointestinal cramping (7, 8). However, there are patients with systemic mastocytosis who have no specific symptoms over years to decades even if the mast cell burden is high.

The D816V *c-Kit* gain-of-function point mutation has been shown to be associated with more than 90% of adult cases of systemic mastocytosis (7, 8). Since its initial description, the diagnostic standard for systemic mastocytosis has been the demonstration of multifocal mast cell clusters of atypical morphology in a bone marrow biopsy specimen (4). This characteristic finding has been accepted as the major diagnostic criterion for mast cell disease (7). The minor diagnostic criteria for the disease include a tryptase level of greater than 20 ng/ml, atypical (spindle shaped, hypogranulated) mast cell morphology, aberrant

expression of CD2 and CD25 on mast cells, and detection of a codon 816 mutation in *c-Kit*. According to WHO guidelines, at least the major criterion plus 1 minor or 3 minor criterion are needed for the diagnosis of mastocytosis (7). Typical skin lesions of urticaria pigmentosa are present in approximately 80% of patients with mastocytosis.

A group of patients with recurrent anaphylaxis have recently been described to have clonal mast cells as demonstrated by evidence of one or more minor criteria for mastocytosis including aberrant mast cell morphology, CD25 expression and/or presence of the *c-Kit* D816V point mutation (10). A recent consensus conference agreed that patients with only one or two minor criteria for mastocytosis have MMAS (8) (Figure 1). The characteristic clinical presentation of these patients includes episodic symptoms of mast cell degranulation, most commonly flushing, lightheadedness and abdominal symptoms such as cramping, nausea and diarrhea. Symptoms may progress to loss of consciousness and life-threatening hypotension. The episodes may last for a few minutes to several hours. There are no identifiable triggers in most patients, although some events have been associated with hymenoptera stings, eating and exercise (with no food-specific IgE). These patients lack characteristic bone marrow mast cell clusters identified in mastocytosis (15 mast cells or greater), and often have normal or only slightly elevated serum tryptase levels. The D816V mutation may be only detectable in a bone marrow sample enriched for mast cells, and not in peripheral blood or unfractionated bone marrow (10). Careful morphologic examination of bone marrow mast cells in Wright-Giemsa stained aspirates or in tryptase stained biopsy sections may reveal hypogranulated and spindle shaped mast cells, which may form small clusters (<15 mast cells) and display blood vessel or bone tropism. These patients thus have a disease process manifesting itself primarily as mast cell activation rather than mast cell proliferation, although they share similar pathologic features. Limited follow up of this patient population thus far has not suggested progression of the extent of bone marrow mast cell infiltration, arguing against the possibility that these findings simply represent an early form of systemic mastocytosis.

Some of these patients may have been diagnosed as having idiopathic anaphylaxis or exercise induced anaphylaxis. There is also convincing evidence that a significant number of patients who experience anaphylaxis with hypotension after hymenoptera stings and have elevated baseline tryptase levels either have (occult) systemic mastocytosis, bone marrow mastocytosis or meet the criteria for MMAS (15).

Diseases associated with secondary mast cell activation

Secondary mast cell activation (Table I) occurs in allergic diseases. Symptoms may be infrequent to frequent and resultant disease sporadic or chronic. Pathology follows aggregation of high affinity IgE receptors by allergen-bound IgE (19). Mast cells are also activated via non-IgE mediated mechanisms including IgG, complement, microbial components, drugs, hormones, physical and emotional stimuli, hormones and cytokines. These mechanisms of mast cell activation are observed in non-allergic inflammatory disorders including chronic autoimmune urticaria; and in physical urticarias (also see Table E3 in the Online Repository). IFN-γ specifically can induce human mast cells to up regulate high affinity IgG receptors, cross linking of which can cause mast cell degranulation (20). This mechanism of mast cell activation may be operational in IFN-γ rich autoimmune disease states such as psoriasis and in inflammatory bowel disease (see Table E3 in the Online Repository). C3a and C5a, activation products of the complement pathway, are capable of activating certain mast cell types (e.g. skin mast cells, mast cells in rheumatoid arthritis) by directly binding to their respective receptors on the mast cell surface (20). Complement-induced mast cell activation may thus contribute to disease symptoms in infectious, autoimmune and neoplastic diseases. Infectious agents also stimulate mast cells directly via toll-like receptors recognizing molecular patterns common to microbial or viral

pathogens (16). Human mast cells have been shown to carry TLR 1–7 and 9 and respond to TLR stimulation by release of cytokines and LTC4 (21). Drugs such as opioid analgesics, adenosine and vancomycin may induce pruritus, flushing and bronchoconstriction by directly activating mast cells. Hypersensitivity reactions to non-steroidal anti-inflammatory drugs inhibiting the cyclooxygenase pathway have been attributed to shifting of arachidonic acid metabolism to the 5-lipoxygenase pathway, causing symptoms due to overproduction of leukotrienes. If use of such a pharmacologic agent is associated with all episodes under question, the diagnosis then is one of an adverse reaction to a drug, not MCAS. However, if the administration of such an agent does not always precede an episode, then the patient could also have MCAS.

Idiopathic mast cell activation

Considering the well established role mast cells play in urticaria, angioedema and anaphylaxis, patients presenting with these disorders, where by definition there is no identifiable etiology, have been included under the idiopathic category (Table I). However, the search must continue for the etiology of these idiopathic disorders including the possibility that mast cell activation in these disorders may relate to a yet-to-be identified endogenous or environmental stimulus and/or intrinsic mast cell defect resulting in a hyperactive mast cell phenotype.

It is also possible that some idiopathic events follow basophil activation rather than mast cell activation, or result from activation of both mast cells and basophils. Selective activation of basophils may be explained by the differential expression of critical cell surface receptors on basophils and mast cells. In fact, some triggers of mediator release may preferentially activate basophils.

Proposed Criteria for the diagnosis of idiopathic mast cell activation syndrome

The presence of a distinct idiopathic MCAS (Table I), where MMAS has been eliminated, has not been universally accepted. Despite the absence of a consensus for objective guidelines for diagnosis, this syndrome is assigned to some patients with a variable number of unexplained signs and symptoms (see Table E1 in the Online Repository); and with an otherwise negative diagnostic workup.

We therefore propose that the diagnosis of MCAS is appropriate when primary and secondary diseases associated with mast cell activation (Table I) are eliminated and if the three additional criteria in Table II are met.

In the proposed diagnostic criteria, patients with a presumptive diagnosis of “MCAS” must have two or more of the organ manifestations of mast cell activation such as flushing, urticaria, diarrhea, wheezing. The diagnosis requires that a patient has evidence of an elevation in mediators such as serum tryptase, 24-hour N-methylhistamine, or 11βPGF2 during at least two episodes with a negative workup for systemic mastocytosis or clonal mast cell disease in bone marrow biopsies; or one episode in patients whose serum tryptase is consistently > 15 ng/ml (8). This requirement for biochemical evidence of mast cell activation is of importance in order to avoid applying the term MCAS to a diagnosis of a disorder unrelated to mast cell pathology but presenting with similar symptoms in the absence of biochemical proof of mast cell activation. Improvement of symptoms with drugs targeting mast cell mediators (such as H1 and H2 antihistamines, cromolyn, leukotriene antagonists) are considered as further supporting evidence of mast cell involvement in the disease process. However, response to anti-mediator therapy, while a diagnostic

requirement, cannot be used alone. For instance, gastrointestinal mast cells degranulate in association with a number of disorders; and antihistamines, cromolyn, and leukotriene antagonists, if effective, do not necessarily implicate mast cells.

Patients presenting with signs and symptoms suggesting MCAS generally have undergone an extensive evaluation to rule out known disease. This being acknowledged, it is always necessary to review medical records of previous evaluations to assure such assessments were sufficient to eliminate from consideration diseases including carcinoid syndrome and other malignant conditions such as pheochromocytoma and medullary thyroid cancer, estrogen or testosterone deficiency, inflammatory bowel disease, autoimmune diseases, reactions to environmental toxins and allergic reactions.

If previous medical evaluations did not identify a basis for the patient's symptoms, systemic mastocytosis or MMAS should then be considered. A careful skin examination should be performed to look for cutaneous mastocytosis including urticaria pigmentosa. A basal serum tryptase level > 20 ng/ml is a minor diagnostic criterion of systemic mastocytosis, and should prompt consideration of systemic mastocytosis in patients who have evidence of mast cell activation. It is also worthy to note that tryptase may be elevated in other hematologic disorders such as chronic eosinophilic leukemia, myelodysplastic syndromes, and acute leukemias (22). Whereas during mast cell activation, tryptase levels increase transiently, the tryptase level in SM and in other myeloid neoplasms is persistently elevated.

A normal tryptase level does not rule out clonal mast cell disease. However, the likelihood of diagnosing mast cell disease by identifying characteristic multifocal bone marrow aggregates diminishes significantly in those with tryptase levels less than 20 ng/ml. Further, the diagnosis of systemic mast cell disease based on biopsies other than bone marrow should generally be avoided. As for a bone marrow evaluation, we are not suggesting that this study be performed in all pediatric patients with UP. This is because the diagnosis of UP establishes a diagnosis of primary mast cell disease, and patients with UP are excluded from being given the diagnosis of MMAS or MCAS. Because of these problems and others, difficult diagnostic cases should be considered for referral to a mast cell disease research and referral center for specialized testing, such as flow cytometry and mutational analysis on marrow enriched for mast cells, approaches that may not be generally available. If clonal markers of mast cell disease are found (i.e. *c-Kit* mutation or aberrant CD25 expression), the patient is assigned a diagnosis of systemic mastocytosis or MMAS depending on the presence or absence of other WHO diagnostic criteria, regardless of presence of a secondary diagnosis which may cause mast cell activation (7, 8). Documentation of mast cell mediator release associated with symptomatic episodes provides critical information to support the premise that symptoms are due to mast cell activation. These tests include serum tryptase (which should be obtained within 4 hours after the onset of symptoms), and 24 urine collections for N-methylhistamine and 11βPGF2. Levels of these mediators during symptomatic periods must be compared with patient's baseline values. Patients with elevated mast cell mediator levels should be carefully evaluated for secondary causes of mast cell activation (Table I). The diagnosis of idiopathic anaphylaxis should be considered in those with recurrent anaphylaxis and no identifiable allergic or clonal mast cell etiology. Because anaphylaxis is a disorder of mast cell activation affecting multiple organ systems, patients with a diagnosis of idiopathic anaphylaxis accordingly also meet the criteria for MCAS. However, not all patients with MCAS need have anaphylaxis. For a comparison of diagnostic criteria for SM, MMAS, MCAS, and IA, see Table E4 in the Online Repository).

Evaluation should include a repeat test of mediator levels after complete resolution of symptoms to determine whether the level returned to the patient's baseline. If clonal markers are absent and a concurrent diagnosis of allergic, inflammatory, infectious or neoplastic

disease is established, then the patient should be considered to have a secondary mast cell activation disorder due to the concurrent illness. Using the approach outlined above, one of us (CA) has reported evidence that such a syndrome exists (23). This study has now been extended using the proposed criteria. Although this data has not yet been published, out of 132 patients enrolled in the protocol, and referred for suspected or confirmed disease over a four year period, 58 met the WHO criteria for systemic mastocytosis 7 for MMAS and 19 for IA. Forty-two patients had mast cell activation symptoms, but no evidence of clonal mast cells. Six patients had another diagnosis unrelated to mast cell disease. While the preponderance of data relates to the adult population, future studies are envisioned where the same criteria could be examined for validity in the pediatric population.

For the future, in validating MCAS as a diagnosis, other evidence of mast cell degranulation in vivo employing such techniques as electron microscopy (24) would be helpful as has been done for exercise-induced anaphylaxis (25).

Summary

We believe that these recommendations for the diagnosis and management of MCAS form a starting point towards a global classification of mast cell disorders in general and MCAS in specific. To be generally acceptable, this classification scheme must be validated and modified by findings from prospective multicenter clinical studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CRH	Corticotropin-Releasing Hormone
DGD2	Diagalactosyldiacylglycerol Synthase 2
FIP1L1-PDGFRA	FIP1-Like 1 Platelet Derived Growth Factor and fusion protein
fMLP	Formyl-Methionyl-Leucyl-Phenylalanine
H1	Histamine H1 Receptor
H2	Histamine H2 Receptor
IA	Idiopathic Anaphylaxis
IFN-γ	Interferon-gamma
ISM	Indolent Systemic Mastocytosis
KIT	CD117, Stem Cell Factor receptor
LAT2	Linker for Activation of T Cells
LTC4	Leukotriene
C4 MC	Mast Cell
MCAD	Mast Cell Activation Disorder

MCAS	Mast Cell Activation Syndrome
MIP1α	Macrophage Inflammatory Protein 1 alpha
MMAS	Monoclonal Mast Cell Activation Syndrome
NGF	Nerve Growth Factor
N-MH	N-methylhistamine
NTAL	Non-T Cell Activation Linker
PDG2	Prostaglandin D2
SCF	Stem Cell Factor
SM	Systemic Mastocytosis
TLR	Toll Like Receptor
UP	Urticaria Pigmentosa
WHO	World Health Organization
α-MSH	Alpha-Melanocyte Stimulating Hormone

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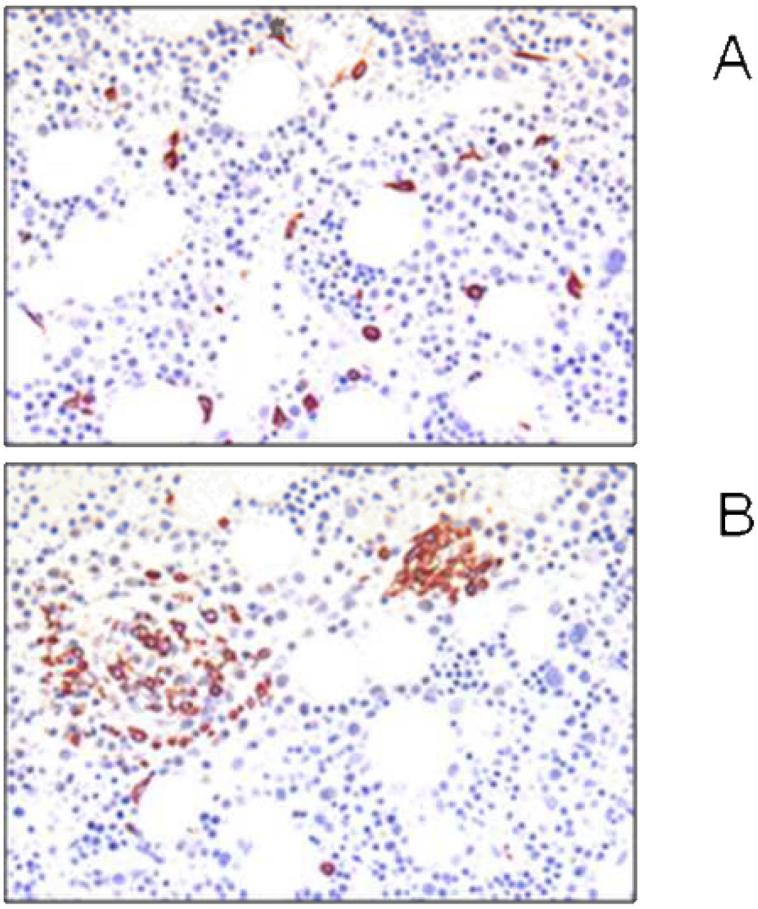

Figure 1.
Bone marrow findings in patients with mast cell activation disorders. In panel A, tryptase-stained bone marrow sections revealed diffusely scattered spindle-shaped mast cells that did not form compact aggregates. In panel B, small-sized multifocal aggregates of mast cells were found, some of which contained 15 mast cells. Mast cells expressed CD25. Findings in panel A are consistent with the diagnosis of a monoclonal mast cell activation syndrome (MMAS), whereas findings in panel B are consistent with the diagnosis of systemic mastocytosis.

Table I

Classification of diseases associated with mast cell activation

1	Primary	
	a.	Anaphylaxis with an associated clonal mast cell disorder
	b.	Monoclonal mast cell activation syndrome (MMAS)*
2	Secondary	
	a.	Allergic disorders
	b.	Mast cell activation associated with chronic inflammatory or neoplastic disorders
	c.	Physical urticarias+
	d.	Chronic autoimmune urticaria
3	Idiopathic#	
	a.	Anaphylaxis
	b.	Angioedema
	c.	Urticaria
	d.	Mast cell activation syndrome (MCAS)~

*See text for explanation

+Requires a primary stimulation

#When mast cell degranulation has been documented; may be either primary or secondary. Note also that angioedema may be associated with hereditary or acquired angioedema where it may be mast cell independent and result from kinin generation.

~See text and Table II for proposed diagnostic criteria

Table II

Proposed criteria for the diagnosis of mast cell activation syndrome*

1	Episodic symptoms consistent with mast cell mediator release affecting two or more organ systems evidenced as follows:
	a. Skin: urticaria, angioedema, flushing
	b. Gastrointestinal: nausea, vomiting, diarrhea, abdominal cramping
	c. Cardiovascular: hypotensive syncope or near syncope, tachycardia
	d. Respiratory: wheezing
	e. Naso-ocular: conjunctival injection, pruritus, nasal stuffiness
2	A decrease in the frequency or severity; or resolution of symptoms with anti-mediator therapy: H1 and H2 histamine receptor antagonists, anti-leukotriene medications (cysLT receptor blockers or 5-LO inhibitor), or mast cell stabilizers (cromolyn sodium)
3	Evidence of an elevation in a validated urinary or serum marker of mast cell activation: Documentation of elevation of the marker above the patient's baseline during a symptomatic period on at least two occasions; or if baseline tryptase levels are persistently >15ng, documentation of elevation of the tryptase above baseline on one occasion. Total serum tryptase is recommended as the markers of choice; less specific (also from basophils) 24 hour urine histamine metabolites, or **11-beta-prostaglandin F2**.
4	Primary (clonal) and secondary disorders of mast cell activation ruled out (Table I).

*Mast cell activation syndrome for now remains an idiopathic disorder; however, in some cases it could be an early reflection of a monoclonal population of mast cells, in which case with time it could meet the criteria for MMAS as 1 or 2 minor criteria for mastocytosis are fulfilled.