Doctor, I Think I Am Suffering from MCAS: Differential Diagnosis and Separating Facts from Fiction

Peter Valent, MD[a], and Cem Akin, MD[b] *Vienna, Austria; and Ann Arbor, Mich*

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List of Design Committee Members: Peter Valent, MD, and Cem Akin, MD (authors); David Khan, MD (editor)

Learning objectives:

1. To be able to apply consensus criteria in the diagnosis of mast cell activation syndrome (MCAS).
2. To be able to establish or exclude a diagnosis of MCAS in all patient groups.
3. To be able to classify MCAS using consensus criteria.
4. To be able to manage patients with MCAS.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: The authors declare that they have no relevant conflicts of interest. D. Khan is on the Aimmune advisory board; has received honoraria from UpToDate; and is a speaker for Genentech.

Mast cell activation syndrome (MCAS) is a rare condition defined by a severe systemic reaction to mast cell (MC)-derived mediators. Most cases present with clinical signs of anaphylaxis, and some have an underlying IgE-dependent allergy. A primary MC disease (mastocytosis) may also be detected. Severe recurrent MCAS episodes requiring intensive care or even resuscitation are typically found in patients who suffer from both mastocytosis and allergy against certain triggers, such as hymenoptera venom components. A less severe form and a local form of MC activation (MCA) also exist. For these patients, diagnostic criteria are lacking. Moreover, a number of different, unrelated, conditions with overlapping symptoms may be confused with MCAS. As a result, many patients believe that they are suffering from MCAS but have in fact a less severe form of MCA or another underlying disease. In the current article, we review the potential differential diagnoses of MCA and MCAS and discuss available diagnostic criteria and diagnostic tools. These criteria and assays may be useful in daily practice and help avoid unnecessary referrals and unjustified fears in patients. **© 2018 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).** **(J Allergy Clin Immunol Pract 2019;7:1109-14)**

Key words: *Mast cells; Mast cell activation; Tryptase; Anaphylaxis; Allergy*

Mast cells (MC) are tissue-fixed multifunctional effector cells of the immune system. These cells produce an array of proinflammatory and vasoactive mediators and cytokines, and

[a]Department of Internal Medicine I, Division of Hematology & Hemostaseology and Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria
[b]Division of Allergy and Clinical Immunology, University of Michigan, Ann Arbor, Mich

This study was supported in part by the Austrian Science Funds (FWF) projects F4701-B20 and F4704-B20.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication October 16, 2018; revised November 26, 2018; accepted for publication November 27, 2018.
Corresponding author: Peter Valent, MD, Department of Internal Medicine I, Division of Hematology & Hemostaseology and Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria. E-mail: peter.valent@meduniwien.ac.at.
2213-2198
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https://doi.org/10.1016/j.jaip.2018.11.045

Abbreviations used
EDS- Ehlers-Danlos syndrome
ISM- Indolent SM
MC- Mast cell
MCA- MC activation
MCAS- MCA syndrome
POTS- Postural orthostatic tachycardia syndrome
SM- Systemic mastocytosis

participate in a number of different pathologic conditions.[1-4] MC also display a range of biologically active receptors, including high-affinity IgE-binding receptors, and are key effector cells of allergic reactions. In mastocytosis, MC and their progenitor cells usually exhibit KIT-activating mutations and expand in a growth factor-independent manner.[5-10] In these patients, the risk for developing severe anaphylactic (hypersensitivity) events is high, especially when a concomitant IgE-dependent allergy is also present.[11-16]

Although MC activation (MCA) is found in many pathologic conditions and disorders, severe forms of MCA are usually observed in patients with IgE-dependent allergies, idiosyncratic or dose-related severe drug reactions, severe forms of food allergy, and in those who suffer from a primary MC disease, usually in the form of a systemic mastocytosis (SM). When the symptoms are severe and recurrent and meet certain criteria confirming systemic MC involvement, the diagnosis MCA syndrome (MCAS) can be established.[17-21]

Symptoms of MCA are frequently recorded in daily practice. However, most symptoms, such as pruritus, headache, flushing, abdominal pain, or tachycardia, are not specific for MCA. Rather a number of other pathologies, such as cardiovascular pathologies, infections, endocrinologic diseases, cutaneous diseases, or gastrointestinal disorders, can mimic MCA.[18-22] It is also worth noting that apart from MC other cell types are often involved in mediator-induced symptoms. In other patients, MCA is a local event (eg, limited to skin or respiratory tract) or an incidental finding.

During the past few years, an increasing number of cases have been referred to specialized centers because of suspected MCAS.[22] In many instances, these patients suffer from an unrelated disease or a less severe or local form of MCA incidentally detected, but do not meet the consensus criteria for MCAS.[22] In the current article, we discuss the necessity of applying current MCAS criteria to confirm the involvement of MC in the symptomatology. We also discuss underlying pathologies, the classification of MCAS, and important differential diagnoses. Finally, we discuss MCA conditions that do not meet MCAS criteria and management recommendations for those who suffer from MCA and MCAS.

DIAGNOSTIC CRITERIA OF MCAS

As mentioned before, an increasing number of patients are referred because they believe or had been informed that they are suffering from MCAS. Many of these patients do not fulfill the criteria of MCAS and do not optimally respond to MCAS therapies. This in turn leads to more frustration in both patients and caregivers as well as to the inappropriate use of health care resources. To assist in these cases, a European/US consensus group has established consensus criteria for the diagnosis of MCAS.[17,18] These consensus criteria are widely accepted and include (1) the episodic (recurrent) occurrence of typical, systemic symptoms that are produced by MC mediators and involve at least 2 organ systems; (2) an increase in mast cell mediators, preferably serum tryptase levels by at least 20% over the individual tryptase baseline plus 2 ng/mL absolute tryptase (eg, from 15 ng/mL baseline to at least $+3 + 2 \Rightarrow 20$ ng/mL; or from 40 ng/mL to at least $8 + 2 \Rightarrow 50$ ng/mL) within a 3-4-hour window after the reaction; and (3) a substantial (documented) response of the symptomatology to drugs that either target MC-derived mediators or their effects (eg, histamine receptor blocker) and/or suppress MC activation.[18] These MCAS criteria have recently been validated and are generally accepted.[22-25]

However, a number of questions remain. First, there are also other MC-derived mediators (eg, histamine, prostaglandin D2 metabolites, or LTE4) that have been proposed as potential laboratory-based criteria of MCAS.[18-22,26-28] Unfortunately, most of these markers are not specific for MC, and the minimal increase in such (urinary or serum) markers other than tryptase, that would meet the diagnostic threshold to diagnose MCAS, remains undefined. For example, PGD2 may be produced by many immune and nonimmune cells, and the specificity of

TABLE I. Classification and variants of mast cell activation syndromes (MCAS)

MCAS variant	Key diagnostic variables
Primary MCAS	*KIT* D816V-mutated clonal mast cells are found; in most cases mast cells also display CD25
Synonyms:	
Clonal MCAS	
Monoclonal MCAS (MMAS)	
(a) With cutaneous mastocytosis (CM)	CM criteria fulfilled; SM criteria not fulfilled
(b) With systemic mastocytosis (SM)	SM criteria fulfilled†
(c) With only 2 minor SM criteria*	Criteria to diagnose CM or SM not fulfilled
Secondary MCAS	An underlying allergy/atopic disorder or other reactive disease process causing mast cell activation and thus MCAS is diagnosed, but no monoclonal mast cells are detected
Idiopathic MCAS	MCAS criteria are fulfilled, but no underlying reactive disease, no IgE-mediated allergy, and no monoclonal mast cells are detectable‡

*Initially described as classical variant of MMAS.
†At least 1 major and 1 minor or 3 minor SM criteria have to be fulfilled to call a condition SM.
‡In these patients, no activating *KIT* mutation at codon 816 is detected, and when tested, flow cytometry usually confirms the presence of CD25-negative (normal) mast cells.

TABLE II. Overview of differential diagnoses to mast cell activation and MCAS

Cardiovascular
Myocardial infarction
Endocarditis/endomyocarditis
Aortic stenosis with syncope
Acute pericardial effusion
Pulmonary embolism
Endocrinologic
Acute hypothyroidism or hyperthyroidism
Acute hypoglycemia
Adrenal insufficiency
Hypopituitarism
Estrogen or testosterone deficiency
Carcinoid
Pheochromocytoma
Medullary thyroid tumor
Gastrointestinal disorders
Inflammatory bowel disease
VIP-secreting tumor (VIPoma)
Acute episode of Crohn's disease or ulcerative colitis
Food intoxication
Irritable bowel syndrome
Mesenteric ischemia
Eosinophilic esophagitis or gastroenteritis
Gastroparesis
Rheumatologic and immunologic disorders
Erythema nodosum
Acute lupus erythematosus
Vasculitis
Systemic capillary leak syndrome
Allergic episodes involving basophils but not mast cells
Less severe conditions associated with mast cell activation
Infectious diseases
Severe bacterial or viral infections ± septic shock
Acute gastrointestinal infection with dehydration
Acute encephalitis/acute meningitis
Acute parasitic diseases (eg, acute Chagas disease)
HLO + gastritis with acute urticaria
Neurologic/central nervous system disorders
Epilepsy
Central nervous bleeding
Intoxication
Multiple sclerosis
Dysautonomia
Psychiatric conditions
Skin diseases
Hereditary angioedema
Acquired engioedema
Pemphigus vulgaris
Lupus erythematodes
Acute toxic dermatoses
Rosacea
Idiopathic flushing
Chronic urticaria
Drug exanthema
Hematologic—acute anemia ± hypovolemic shock
Acute gastrointestinal bleeding
Massive hypermenorrhea
Peripheral T-cell lymphoma with pruritus + rash

HLO, *Helicobacter pylori*; *MCAS*, mast cell activation syndrome; *VIP*, vasoactive intestinal peptide.

elevation in other diseases is not known. Another question relates to the time interval that is required to diagnose MCAS. In fact, the serum tryptase result and the response to immediate therapy have to be awaited before a diagnosis of MCAS can be established. Therefore, the immediate diagnosis of anaphylaxis is established first, and only the consecutive evaluation will (or will not) confirm MCAS. Here, we propose that the provisional diagnosis of "probable MCAS" can be established (without demonstrating an increase in tryptase) when typical symptoms of anaphylaxis are found. Another important point is that also other drugs (not only antimediator-type or MC-stabilizing drugs) and their efficacy may count as a sign of MC involvement and thus MCAS, provided that other MCAS criteria are also fulfilled. For example, drugs reducing MC numbers (eg, KIT tyrosine kinase blocker) or removing IgE (eg, omalizumab) may also reduce symptoms and may thereby support the conclusion that MC and/or IgE are involved and thus the patient is suffering from MCAS.

CLASSIFICATION OF MCAS

Based on the underlying etiology and the consensus proposal, MCAS can be classified into primary (clonal) MCAS, secondary MCAS, and idiopathic MCAS (Table I).[18] In primary MCAS, clonal MC are detected. Most of these patients are suffering from an underlying clonal MC disease, usually in the form of SM.[18] In a majority of these cases, the *KIT* mutation D816V is detected and MC display CD25. In a few cases, clonal (*KIT* mutated) MC are found, but the criteria sufficient to diagnose SM are not fulfilled.[17,18,29,30] As per definition, these patients are also suffering from clonal (primary) MCAS, also termed monoclonal MCAS (MMAS) (Table I).[17,18] In some of these cases, SM is diagnosed in the follow-up or is detected when BM investigations are repeated. Most patients diagnosed with secondary MCAS are suffering from an underlying IgE-dependent allergy. However, in some cases, an IgE-independent allergy or a suspected but not confirmed allergy (no allergen and/or specific IgE against allergens detected) is present.[17-20] In rare cases, an autoimmune disorder, chronic infection, or neoplastic or preneoplastic disorders are detected. When no underlying condition is found, the diagnosis is idiopathic MCAS.[17-20] It is important to be aware that a patient may suffer from both a primary and secondary MCAS, which is a high-risk situation. As an example, some patients may have SM as well as a bee or wasp venom allergy.[14,15,31-33] These patients usually require specific therapy. In particular, in addition to treatment with antimediator-type drugs, these patients often need specific (lifelong) immunotherapy or treatment with omalizumab.[17-20,31-37]

TABLE III. Conditions associated with an elevated basal serum tryptase level

Diagnosis	Origin/cellular source of tryptase
Hematologic	
Systemic mastocytosis	Neoplastic mast cells
Chronic myeloid leukemia	Leukemic (immature) basophils
Chronic eosinophilic leukemia	Neoplastic mast cells
Chronic basophilic leukemia	Leukemic (immature) basophils
Acute basophilic leukemia	Leukemic (immature) basophils
Acute myeloid leukemia	Blast cells
Myelodysplastic syndrome (MDS)	Blast cells, basophils, mast cells
Myeloproliferative neoplasm (MPN)	Blast cells, basophils, mast cells
MDS/MPN overlap neoplasm	Blast cells, basophils, or mast cells
Myelomastocytic leukemia	Blast cells and neoplastic mast cells
MPN-eo with mutated *PDGFR* or *FGFR*	Neoplastic mast cells
Nonhematologic reactive	
Atopic disorders (allergy)	Mast cells
Chronic worm infections	Mast cells
Other etiologies	
End-stage kidney disease (renal failure)	Mast cells
Familial (hyper) (alpha) tryptasemia*	Mast cells, other cells?
Healthy individuals	Mast cells?
False positive result†	

*In these individuals, the *TPSAB1* gene encoding alpha tryptase is expressed in 2 or even multiple copy numbers.[44]

†False positive results had been discussed in the context of the presence of heterophilic antibodies, but the new generation of test assays should avoid this problem.

DIFFERENTIAL DIAGNOSES

A number of different clinical conditions and disorders can mimic MCAS.[17-20] Typical differential diagnoses are cardiac disorders (myocardial infarction, myocarditis), septicemia (eg, bacterial sepsis), pharmacologic side effects (eg, hypotension with antihypertensive drugs, tachycardia and gastrointestinal hypomotility with antihistamine overdose, flushing and skin rashes with glucocorticosteroids), dehydration with hypovolemic shock, and endocrinology emergencies (eg, adrenal crisis) (Table II).[18-21] In other patients, one or more of the following symptoms are found: acute skin rash, chronic flushing, headache, gastrointestinal cramps, and diarrhea. Such symptoms may be histamine-induced and thus point at an unrecognized MCAS. However, there are a number of differential diagnoses that have to be considered, including skin disorders (eg, atopic or contact dermatitis, rosacea), endocrine disorders (eg, thyroid disease, estrogen or testosterone deficiency, adrenal insufficiency, carcinoid), neurologic disorders (eg, seizures, stroke, multiple sclerosis, meningitis, dysautonomia, vasovagal syncope), psychologic disorders (eg, panic attacks and anxiety, depression), or gastrointestinal diseases such as an inflammatory bowel disease (Table II). Finally, even acute allergic reactions and related symptoms may mimic MCAS. In these patients, the criteria for MCAS are not met because the reaction is not severe enough or because mostly basophils but not MC (or only few MC) are involved. Some patients may have concurrent atopic disorders (which may affect up to 20% of the population), dermographism, or urticaria but not systemic MCAS. In these cases, histamine metabolites and/or PGD2 metabolites may increase, but other MC-specific markers such as the serum tryptase are not or only slightly elevated over the individual baseline when measured during the event.[27,28] Patients with hyperadrenergic form of postural orthostatic tachycardia syndrome (POTS) and hypermobility-type Ehlers-Danlos syndrome (EDS) have also been discussed to suffer from symptoms resembling or mimicking MCA or even MCAS, but objective evidence to incriminate MC in their pathology has been lacking.[38] Rather, MCAS defined by consensus criteria has not been reported to occur typically in patients with POTS or EDS. A summary of differential diagnoses to MCAS is shown in Table II.

PRACTICAL APPROACH AND ADVICE TO DOCTORS

Most patients with MCAS suffer from recurrent episodes of severe hypotension (anaphylaxis). If this is not the case, MCAS may still be diagnosed, but is a less likely diagnosis. In particular, there is no evidence to support the existence of a chronic form of systemic MCAS without severe episodic events. Patients with multiple chemical and environmental intolerances or multiple food intolerances should not be diagnosed as MCAS. A detailed physical examination should be performed in all cases. Such examination may reveal typical skin lesions of mastocytosis, a generalized rash or signs of atopic dermatitis. After having eliminated key differential diagnoses, the doctor may come to the conclusion that the patient may suffer from an MCA-related condition or even MCAS. In the next step, the physician will explore whether the reaction is systemic and involves 2 or more organ systems, whether the symptomatology is episodic and recurrent, and whether the event(s) can be related to MC and MC-derived mediators. The latter is of great importance and requires the measurement of the baseline- and event-related level of MC-specific compounds, such as the serum tryptase. When the tryptase level increases substantially during an attack, the reaction can be regarded as MCA-related.[18-20,24,25] When the reaction is not severe and the serum tryptase does not increase over the individual's baseline during the event, the patient may still suffer from MCA and an IgE-dependent reaction, but the likelihood of MCAS is very low. In the next step, the diagnosis of MCAS can be confirmed by demonstrating an improvement of the symptoms (and a prophylactic effect) of drugs directed against MCA or against MC mediator-induced effects, for example, histamine-induced symptoms using histamine receptor blockers.[18-20]

Finally, after having confirmed the presence of MCAS, the underlying etiology should be defined. As mentioned before, patients with MCAS may suffer from an IgE-dependent allergy and/or an underlying mastocytosis.[18-20] Moreover, these patients may suffer from intoxications, food intolerance, or an autoimmune disorder. When no underlying disease is detected, the doctor will establish the diagnosis of an idiopathic MCAS (Table I).

WHAT IF MCA IS PRESENT BUT CRITERIA TO DIAGNOSE MCAS ARE NOT FULFILLED?

In many cases, signs and symptoms typical for MCA are identified, but the criteria of MCAS are not met. These are patients who present with severe symptoms of anaphylaxis but did not respond to mediator-targeting drugs or did not show a diagnostic increase in tryptase. In others patients, tryptase levels increase slightly but the diagnostic increase and thus the criteria of MCAS are not fulfilled. In these patients, it may be reasonable to measure other relevant mediators, such as histamine, PGD2 metabolites, or LTE4.[18-20,26-28] If in such cases, a major increase of such metabolites is found and the symptoms respond to histamine receptor blockers and/or arachidonic acid synthesis inhibitors, the diagnosis of MCAS can also be considered, although these mediators can also be derived from other cells.[18-22]

As mentioned before, there are also patients in whom the symptoms are less severe and/or only restricted to 1 local organ site. In these cases, it is reasonable to ask for MCAS criteria, but in most of these patients, it will turn out that they are suffering from either an unrelated disease (condition) or a less severe form of MCA.[18-22] Atopic disorders are common in the general population and may present as a comorbidity unrelated to global symptomatology of the patients.

A special situation is SM with MCA not fulfilling MCAS criteria. The recommendation of the consensus group is that in such patients, any type of MCA requiring continuous antimediator-type drugs should be marked with the diagnostic label "SY" appearing as a subscript to SM (SM_{SY}).[18] Patients diagnosed with SM_{SY} may have MCAS but may also suffer from MCA-related symptoms requiring therapy without meeting MCAS criteria. *Example*: in a patient with indolent SM (ISM) requiring continuous histamine receptor blockers and glucocorticosteroids to control MCA-related events like hypotension and/or flushing, the final diagnosis should be ISM_{SY} even if MCAS criteria were not fulfilled (eg, no event-related, diagnostic increase in tryptase over baseline found) or were not documented.

In a number of different conditions, the basal serum tryptase level is slightly elevated (Table III).[39-46] Such elevation is not necessarily associated with an increased risk to develop MCA or MCAS. Rather, an increased basal tryptase level can be detected in healthy individuals, in those who have familial hypertryptasemia, in patients with asymptomatic SM, and in those who are suffering from a clonal myeloid non−MC-lineage neoplasm, such as a myeloid leukemia.[39-46] In addition, slightly elevated basal tryptase levels are detectable in patients with end-stage kidney disease and those who suffer from chronic worm infection.[41] In patients with familial hypertryptasemia, germline copy number variants of the *TPSAB1* gene encoding alpha tryptase have recently been identified.[44-46] In these patients, tryptase levels are increased proportionately to the number of alpha tryptase gene copies. These patients have slightly increased numbers of bone marrow mast cells, but so far no evidence has been presented to prove that mast cells carrying additional alpha tryptase alleles have a hyperactivated phenotype. In some of these patients, mediator-related symptoms have been described, but severe symptoms fulfilling MCAS criteria are unusual and may point to the concomitant presence of an underlying allergy or an underlying clonal MC disease. Clinical phenotypes of these patients need to be analyzed and confirmed in large cohorts.

PRACTICAL ADVICE FOR AFFECTED INDIVIDUALS

As mentioned before, more and more patients are being told by their physicians that their symptoms are due to MC activation or MCAS.[22] Others believe that they could suffer from MCAS when they undergo self-evaluation based on questionnaires provided in the internet. However, in many if not most instances, the symptomatology that is produced by the patients (and is reported by patients to doctors) does not meet the consensus criteria of MCAS.[22] Rather, these patients suffer from other (often undetected) problems or conditions or they suffer from a less severe form of MCA. To assist in this situation, we recommend the following questions to be answered by patients who were informed to (probably or maybe or definitively) suffer from MCAS:

(1) Did my symptoms repeatedly occur in the form of severe attacks requiring immediate medical intervention and/or hospitalization?
(2) Did my symptoms lead to an anaphylactic shock requiring hospitalization?
(3) Did my doctor(s) measure serum tryptase levels before, during, and after my attacks?
(4) Did my doctor(s) tell me that my tryptase levels increased during my attacks?
(5) Did my symptoms improve with continuous treatment with antihistamines?
(6) Did the frequency of severe attacks decrease since I took steroids or antihistamines?
(7) Did my doctor(s) diagnose an IgE-dependent allergy?
(8) Did my attacks resolve or decrease in number after I started with omalizumab?

When most of these questions are answered with "yes," the likelihood of MCAS is rather high. When most of these questions are answered with "no," an MCAS can essentially be ruled out or is very unlikely. When no severe attacks (with hypotension and shock) were recorded, the probability of MCAS is in general very low.[22] Patients with mastocytosis and/or a documented IgE-dependent allergy are at a higher risk of developing an MCAS. However, MCAS should not be established as a diagnosis of exclusion and based on symptoms alone.

SUMMARY AND FUTURE PERSPECTIVES

MCAS is a well-defined rare condition that occurs most frequently in patients with IgE-dependent allergies and/or SM, but can rarely also occur on the basis of other conditions. In a few cases, no underlying disease is found leading to the diagnosis of "idiopathic MCAS." Diagnostic MCAS consensus criteria have been established and should be employed in each case. When patients with suspected MCAS are referred, it is important to use these criteria and to follow the related diagnostic algorithm to differentiate between true MCAS, other MCA-related disorders, and unrelated conditions where MC are not involved. A key diagnostic marker is the event-related increase in MC tryptase over the individual's baseline, measured in the symptom-free interval. When the tryptase elevation exceeds a certain threshold (20% from baseline plus 2 ng/mL) the diagnosis of MCAS is very likely. Less severe and localized forms of MCA do not fulfill MCAS consensus criteria but may also be relevant

clinically and require attention by the treating physician. In addition, a number of conditions and disorders can mimic symptoms of MCA or MCAS. These conditions have to be considered in each case, especially when MCAS criteria are not fulfilled. This is important as some of these differential diagnoses are serious or even life-threatening and thus need to be identified instead of misdiagnosing the case as MCAS.

Acknowledgments

Both authors contributed substantially to the study by establishing the concept and by writing parts of the manuscript. Both authors approved the final version of the document.

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