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Selecting the Right Criteria and Proper Classification to Diagnose Mast Cell Activation Syndromes: A Critical Review

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In recent years, knowledge about mechanisms underlying mast cell activation (MCA) and accumulation in various pathologic conditions increased substantially. In addition, criteria and a classification of MCA syndromes (MCASs) have been set forth. MCAS is defined by typical clinical symptoms, a substantial increase in serum tryptase level during an attack over the patient's baseline tryptase, and a response of the symptoms to drugs targeting mast cells, mediator production, and/or

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Abbreviations used
BM- Bone marrow
CM- Cutaneous mastocytosis
HαT- Hereditary α-tryptasemia
IA- Idiopathic anaphylaxis
MC- Mast cell
MCA- Mast cell activation
MCAD- Mast cell activation disorder
MCAS- Mast cell activation syndrome
REMA- Red Española de Mastocitosis
sAT- Acute serum tryptase
sBT- Serum baseline tryptase: SM— Systemic mastocytosis

mediator effects. Alternative diagnostic criteria of MCAS have also been suggested, but these alternative criteria often lack specificity and validation. In this report, we critically review the contemporary literature relating to MCAS and compare the specificity, sensitivity, and strength of MCAS-related parameters within proposals to diagnose and classify MCAS and its variants. Furthermore, we highlight the need to apply specific consensus criteria in the evaluation and classification of MCAS in individual patients. This is an urgent and important medical necessity because as an increasing number of patients are being given a misdiagnosis of MCAS based on nonspecific criteria, which contributes to confusion and frustration by patients and caregivers and sometimes may delay recognition and treatment of correct medical conditions that often turn out to be unrelated to MCA. **(J Allergy Clin Immunol Pract 2021;■:■-■)**

Key words: *Mast cells; MCAS; Tryptase; Hereditary alpha Tryptasemia; Mastocytosis; Anaphylaxis; Vienna consensus criteria*

INTRODUCTION

Mast cells (MCs) are granulated, multifunctional effector cells of the immune system that are found in all vascularized tissues.[1-5] Upon stimulation, MCs secrete proinflammatory and vasoactive mediators.[6,7] Several of these mediators contribute to physiologic processes and maintenance of tissue homeostasis.[8] Mast cells constitutively display a number of clinically relevant receptors, such as the high-affinity receptor for IgE (FcεRI), stem cell factor receptor (KIT [CD117]), and cell-surface G protein-coupled receptors, including the Mas-related G protein receptor-X2 (MRGPRX2).[7,9-12]

Mast cells have been implicated in the pathogenesis of a broad range of disorders and conditions related to MC activation (MCA).[4,13] Severe forms of MCA (anaphylaxis) are usually observed in patients with IgE-dependent allergies and those with clonal MC disorders.[13-15] The severity of MCA depends on several factors, including the type of allergen, the route of exposure, augmenting factors, comorbid conditions, the presence of clonal MC, and genetic background. In patients with clonal MC, IgE-dependent and IgE-independent MCA reactions may be severe (often in the form of anaphylaxis), depending on both the inherent hyperreactivity of MCs and the disease context, including the possible occurrence of IgE-dependent allergies as well as other hypersensitivity disorders.[16-18] Notably, MCs are major effector cells of anaphylaxis in humans.[19] Independent of the clinical diagnosis, severe MCA (anaphylaxis) often involves two or more organ systems, although it may present primarily as hypotension leading to anaphylactic shock.[20,21] In patients with systemic mastocytosis (SM), the risk for developing severe or even life-threatening anaphylaxis is high, especially when a concomitant IgE-dependent allergy or the genetic trait Hereditary α-tryptasemia (HαT) is present.[22-25]

When MCA-related symptoms are severe and recurrent, the diagnosis of MCA syndrome (MCAS) may be considered.[26-30] A first description of MCAS was provided by Akin et al[26] in 2010. Subsequently, a meeting of experts representing the fields of allergy, immunology, dermatology, and hematology resulted in consensus criteria and a consensus classification of MCAS (Vienna consensus).[28] This consensus group concluded that MCAS is a heterogeneous disorder, and that its diagnosis should be rendered only when specific diagnostic criteria for MCAS are met.[28-30]

Of note, the terms "MCA disorders" (MCAD) and "MCAS" have sometimes been used interchangeably. However, there is still no consensus definition of MCAD. Nonetheless, MCAD is sometimes used to refer to all disorders associated with MCA; as such, it would encompass a yet to be defined broader definition, whereas MCAS is reserved for patients with severe acute systemic manifestations meeting MCAS criteria.

More recently, and specifically, confusion has resulted from publication of alternative criteria related to the diagnosis of MCAS.[31] These criteria are much broader and less specific for MCA or MCAS.[31-34] Such alternative approaches with less stringent criteria result in an expanding group of individuals being labeled as having MCAS, but who exhibit a wide and nearly unlimited range of symptoms claimed to be attributable to MCA without clear relation to MCs or attributes of anaphylaxis or MCA. Thus, an increasing number of patients who believe that they are, or have been informed that they are, experiencing MCAS are being referred to specialized centers.[28] In many instances, these patients have an unrelated disease, do not fulfill the classical stringent Vienna consensus criteria of MCAS, and thus fail to respond to MCAS therapies.[28] This has resulted in an increasing demand for health care resources.

This review was prepared by a panel of European Union and US experts in the field to convey the importance of applying evidence-based consensus MCAS criteria to confirm the systemic involvement of MCs and their activation in the symptomatology, and to avoid overdiagnosis or misdiagnosis. Also discussed are underlying pathologies, the criteria and classification of MCAS, important differential diagnoses, and other MCA conditions that do not meet consensus MCAS criteria. In addition, the clinical impact of the recently recognized genetic trait HαT is discussed.

DIAGNOSTIC CRITERIA OF MCAS AFTER THE VIENNA CONSENSUS

The Vienna consensus criteria were established by a group of clinical experts from various fields and disciplines in 2012.[28] These criteria remain valid and were reconfirmed in 2019 with minor modifications.[30]

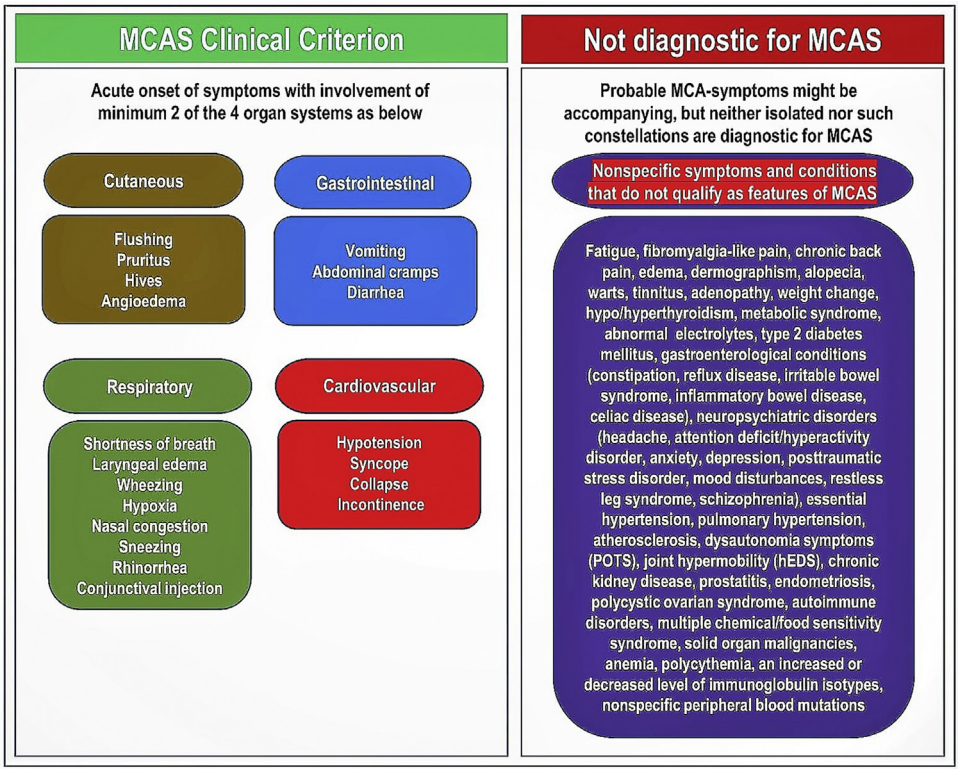

FIGURE 1. Clinical criterion of mast cell activation syndrome (MCAS). Features that qualify as MCAS criteria are shown in the left box and those that do not justify MCAS in the right box. In the left box, typical clinical signs of acute, severe, recurrent (episodic) systemic mast cell activation (MCA) (in form of anaphylaxis) involving at least two organ systems that qualify as MCAS criteria are illustrated. All of these organ systems may be involved in anaphylaxis, with typical, recurrent clinical symptomatologies. In addition to these clinical criteria, objective laboratory evidence of mast cell (MC) involvement by confirming a substantial transient increase in validated MC mediators and control of symptoms with MC-directed therapies is required to fulfill MCAS criteria so that the diagnosis MCAS can be established. Clinical features shown in the right box are not specific for MC activation and are usually reported as a chronic rather than acute manifestation. Therefore, in neither isolated nor combined form may such symptoms qualify as MCAS criteria. Notably, concurrent occurrence of hypermobile Ehlers-Danlos syndrome (hEDS), postural orthostatic tachycardia syndrome (POTS), and MCAS was postulated; however, to date, a relationship among these conditions has not been definitively proven.

The definition of MCAS after the Vienna consensus is based on three diagnostic criteria that have to be fulfilled before the diagnosis of MCAS can be established: (1) typical (MCA-related) clinical symptoms; (2) an event-related increase in serum tryptase above the individual's baseline tryptase (sBT), according to the formula: sBT + 20% of sBT (= 120% of sBT = sBT × 1.2) plus 2 ng/mL; and (3) response to drugs directed against MCA or the production or effects of MC mediators.

Clinical criterion

Severe, episodic, and recurrent symptoms induced by MC mediators with concurrent involvement of at least two organ systems are required to meet the clinical consensus criterion of MCAS.[28-30] The most frequently reported symptoms of MCAS encompass cardiovascular, cutaneous, gastrointestinal, respiratory, and naso-ocular symptoms.[28-30,35] (Figure 1). Mast cell activation syndrome events usually satisfy the clinical criteria of anaphylaxis. For instance, concurrently occurring symptoms such as flushing and hypotensive syncope are highly suggestive for MCAS.[29,30] Conversely, less severe (often chronic) symptoms or localized forms of MCA (ie, limited to skin or respiratory tract, such as chronic urticaria or uncontrolled asthma) do not qualify as diagnostic criteria of MCAS.

Laboratory criterion

The Vienna consensus requires clinical symptoms of MCAS to be associated with an acute, event-related increase in the levels of a validated marker of systemic MCA. Criteria for the diagnosis of MCAS in which such biochemical markers and their event-related increase are not included have the problem that MCA is not objectively confirmed, and thus a distinction cannot be made in the differential diagnoses between MCAS and other conditions. Moreover, it is important to select the most reliable MC-specific marker that is available. The acute serum tryptase (sAT) level, when significantly elevated from the individual's baseline, is a specific marker for MCA and thus MCAS, although sensitivity varies with the severity of the reaction and timing of collection. By contrast, other MC-related markers are less specific and less well (or not yet) validated. Table I lists MC mediators for which there is substantial evidence for their contribution to MCA-related symptoms and their potential clinical utility as diagnostic parameters in suspected MCAS. However, elevated mediator levels should be evaluated in the appropriate clinical

context, and results should be compared during symptomatic episodes and in the asymptomatic intervals (baseline) to confirm the diagnosis of MCAS.[28-30]

Serum tryptase levels serve as the most specific marker and gold standard for measuring the MC burden (sBT) as well as MCA and thus MCAS (sAT over sBT).[28-30,36-38] The tryptase level usually increases during substantial systemic MCA/degranulation, peaks in serum about 1 hour after clinical onset of the event, and then declines with a half-life of about 2 hours, and may remain elevated 4 hours or longer, depending on the magnitude of the initial elevation.[39,40] In healthy individuals with normal tryptase gene copy numbers, the sBT level is generally below 8 ng/m. When greater than 11.4 ng/mL, the sBT is considered elevated, and a level greater than 20 ng/mL is a minor diagnostic criterion for SM.[41] According to the consensus criteria for the diagnosis of MCAS, sAT should be greater than sBT $\times$ 1.2 + 2 ng/mL to confirm the presence of MCAS.[28-30,42] This approach has been validated and is broadly accepted.[43,44] Some drawbacks in clinical practice may occur (eg, if acute sample collection is overlooked or delayed). If no previous sBT is available, such measurement should be determined in serum collected after a minimum interval of 24 to 48 hours after complete recovery from a putative MCA episode.[36-38] Of note, a normal sBT level does not exclude MCAS, whereas a high sBT alone is not an indication or criterion of MCAS.

Mediators other than tryptase are less specific for MCs and MCAS; limited data are available to establish cutoffs for a significant increase in the levels of these mediators that would qualify as reliable indicators of severe systemic MCA.[45-50] Although 24-hour samples of urinary mediators are preferred, shorter collection times or spot analyses have also been described.[50,51] Among those, urinary metabolites of histamine, *N*-methyl histamine, and 1-methyl-4-imidazole acetic acid, are the most commonly measured and have been reported to correlate with MC burden and MCA.[50,52-54] Measuring plasma histamine levels as a marker of MCA is not generally recommended, and urinary histamine and histamine metabolite levels may be influenced by bacterial flora of the urinary tract, storage conditions, and diet.[55]

Prostaglandin D_2 (PGD_2) is a well-known product of activated MCs.[46,49,50,56-59] Studies have shown that during anaphylaxis, as well as in patients with SM, levels of the PGD_2 metabolite 9α-11β-PGF_2 in urinary samples are elevated compared with healthy controls.[50,60,61] However, in most studies, event-related increases in PGD_2 have not been reported, because samples are rarely collected during events. In addition, PGD_2 is also produced and released by other cell types.[62-65] Thus, although rare, elevations in PGD_2 might be caused by pathologic processes independent of MCs and thus MCA. In addition, leukotriene C_4 is a lipid mediator that is released during MCA and undergoes metabolism into leukotriene D_4, which is then converted to leukotriene E_4.[66,67] Urinary leukotriene E_4 was reported to be higher in patients with anaphylaxis who developed severe hypotension, and also in patients with SM, although the degree of elevation correlating with MCAS has yet to be defined.[6,47,51,52,58,66,68-70]

Other potential markers that have been discussed in the context of MCA include heparin, serotonin, neuropeptides, platelet-activating factor, and chromogranin A (CgA).[13,71-76] However, there are insufficient data to demonstrate their clinical utility in the diagnosis of MCA and MCAS. For instance, serum levels of CgA have been reported to be fairly specific to MCs; however, there is no study providing evidence that human MCs are a relevant source for CgA. Moreover, the use of proton pump inhibitors may be associated with elevated serum CgA in patients with mastocytosis; however, this finding does not correlate with MC burden or activation.[75] Thus, CgA levels are not elevated in patients with mastocytosis.[75]

Therapeutic response criterion

Another required criterion of MCAS is a documented therapeutic response to specific drugs that target MC-derived mediators or mediator effects and/or suppress MCA[28-30] (Table I). These drugs include antihistamines, leukotriene modifiers, cyclooxygenase inhibitors, and MC-stabilizing agents. It is advisable to use a stepwise approach to treat MCAS patients. Optimally, the therapy should target the elevated mediators and control symptoms at the lowest effective dose.[77-80] When available, measurement of the urinary mediators (both at baseline and during the flares) is worthwhile because it enables the specific mediator(s) causing the symptoms to be targeted. These therapies are expected to cause significant relief of symptoms and decrease the frequency and severity of MCA events, although they may also alleviate symptoms when these mediators are produced by non-MCs.

Response to additional drugs, including multitargeted tyrosine kinase inhibitors (in patients with SM, such as midostaurin) and anti-IgE therapy (ie, omalizumab) may be considered an indirect sign of MCA or MCAS.[80-88] Agents targeting growth and activation of neoplastic MCs, such as KIT-targeting kinase blockers, are often recommended in advanced SM.[89-92] For instance, midostaurin is a broadly acting signal transduction inhibitor that recognizes kinase targets (such as SYK) downstream of the IgE receptor.[93,94] Therefore, these agents may help to control MCA in patients with advanced SM.[94] Reducing free IgE levels with omalizumab leads to a reduction in FcεRI expression on MCs, reducing the activatability of these cells by FcεRI-dependent pathways, which might be helpful in some patients with MCAS.

Overall, we recommend that all three consensus MCAS criteria be fulfilled before the diagnosis of MCAS is established. We strongly believe that the following remarks are of paramount importance in considering a diagnosis of MCAS.

WHY DO ONLY EVENT-RELATED CHANGES IN MC MEDIATORS FROM THE INDIVIDUAL'S BASELINE BUT NOT BASELINE LEVELS OF THESE MARKERS QUALIFY AS CRITERIA FOR MCAS?

Some individuals have proposed that indicators of the presence of clonal MCs and/or an elevated sBT or other MC-derived mediators can serve as criteria for MCAS.[31,32,34] However, MC clonality or a persistently increased sBT level (or PGD_2 or histamine metabolites) is not necessarily associated with MCA even if the levels are high. For example, patients with SM, in whom high numbers of clonal MCs are detectable, can be asymptomatic over time without MC activation even if the sBT level (stably) exceeds 100 ng/mL. Also, patients with HαT may have elevated sBT levels in the absence of MC activation symptoms. Therefore, only an event-related significant increase in tryptase (or another MC mediator) over the individual's baseline (sBT) together with typical clinical symptoms qualify as MCAS criteria. Similarly, the

TABLE I. Mast cell mediators and common clinical symptoms attributable to severe mast cell activation

Organ systems	Clinical features	Attributed mediators	Possible therapeutic interventions
Cardiovascular	Tachycardia Light-headedness Hypotension Syncope	Histamine, PGD_2, PAF, cysteinyl LTs	In emergency: Epinephrine In prevention: HR1- and HR2-antihistamines Antileukotrienes Omalizumab Lifelong insect venom immunotherapy, if relevant
Cutaneous	Urticaria Angioedema Flushing Pruritus	Histamine, PGD_2, PAF, cysteinyl LTs	HR1- and HR2-antihistamines Ketotifen Rupatadine Aspirin or NSAID Omalizumab
Digestive	Abdominal cramps Diarrhea Vomiting	Histamine, cysteinyl LTs, PAF	HR2-antihistamines Cromolyn sodium (oral formulation) Glucocorticoids
Upper/lower respiratory	Nasal congestion Sneezing Shortness of breath Wheezing Inspiratory stridor Hypoxia	Histamine, PGD_2, PAF, cysteinyl LTs	HR1-antihistamines Antileukotrienes Cromolyn sodium (nasal spray) Nasal steroids Inhalation steroids if asthma diagnosed Omalizumab

presence of an activating *KIT* mutation or expression of CD25 can document MC clonality but these are neither biomarkers of MCA nor criteria of MCAS, because many of these patients remain asymptomatic.

WHY IS THERE A NEED TO INTRODUCE A FLEXIBLE SLOPE-BASED EQUATION TO DIAGNOSE MCAS?

Baseline values of MC mediators vary among individuals, depending on their genetic background, underlying disease, and comorbidities. For instance, sBT levels may be elevated in HαT, SM, other myeloid neoplasms, end-stage kidney disease, and obesity.[95,96] In addition, there are individuals with a low sBT level, and when these patients develop MCAS, the event-related increase in tryptase may remain below 11.4 ng/mL. Therefore, it is crucially important to use a flexible and individually adjusted formula that defines a diagnostic threshold increase in tryptase qualifying as an MCAS criterion (>sBT × 1.2 + 2 ng/mL). The same will apply for other MC mediators that may qualify as indicators of MCAS once these mediators have been validated.

WHY ARE STATIC BIOCHEMICAL MARKERS, GENETIC MARKERS, OR MARKERS OF MC CLONALITY NOT USEFUL AND NOT RECOMMENDED AS CRITERIA FOR MCAS?

Mast cell activation syndrome is composed of a heterogeneous group of conditions for which patients be given a diagnosis only according to Vienna consensus MCAS criteria. For instance, an individual patient can concomitantly fulfill criteria for SM as well as MCAS. Although a bone marrow (BM) biopsy is important to confirm the diagnosis of SM in these patients, histopathologic and immunohistologic findings, *KIT* D816V mutational analysis, or consistently increased sBT levels alone are insufficient to diagnose MCAS.

Thus, the documented presence of clonal MCs alone or the diagnosis CM or SM alone are not an indication of MCAS, even though such patients are at increased risk for developing MCA-related events that could lead to the diagnosis of MCAS. Laboratory strategies for assessing MCA lack credibility if they do not use an event-related rapid and transient increase in the levels of a specific MC mediator, and should not be employed to diagnose MCAS. In addition, the clinical symptoms used to define MCAS must be related to MC-dependent features. Otherwise, most patients with SM and many with unrelated disorders would be given the incorrect diagnosis of MCAS.

CLINICAL PHENOTYPES OF MCAS

Based on the Vienna consensus, MCAS can be divided into primary (clonal) MCAS, secondary (nonclonal) MCAS, and idiopathic MCAS (Figure 2).[28,30] The mechanisms that activate MCs in different MCAS phenotypes may differ. However, the clinical symptoms usually overlap, because triggers leading to the manifestations of MCAS are often the same. Primary MCAS includes conditions characterized by MCAS criteria and a population of clonal MCs exhibiting an activating mutation in *KIT*, usually *KIT* D816V, and/or aberrant expression of CD25.[28] Thus, the diagnosis of (mono)clonal MCAS can be made only when (1) consensus MCAS criteria are fulfilled, and (2) a population of monoclonal MC can be detected. In most of these patients, CM or SM is diagnosed (Figure 2). Rarely, only one or two SM criteria indicating the existence of clonal MCs (ie, displaying CD25 and/or *KIT* D816V mutation) but no CM or SM are found in patients with primary MCAS.

In patients with secondary MCAS, MCs are normal (nonclonal) cells even if they are sometimes slightly elevated in tissue sections (reactive).[16,97] These patients usually have an IgE-dependent allergy or another hypersensitivity disorder. The inciting trigger for MCA in secondary MCAS can be IgE-mediated (food, drug, Hymenoptera venom, or inhalant allergen) or non−IgE-mediated (endogenous peptides or drugs

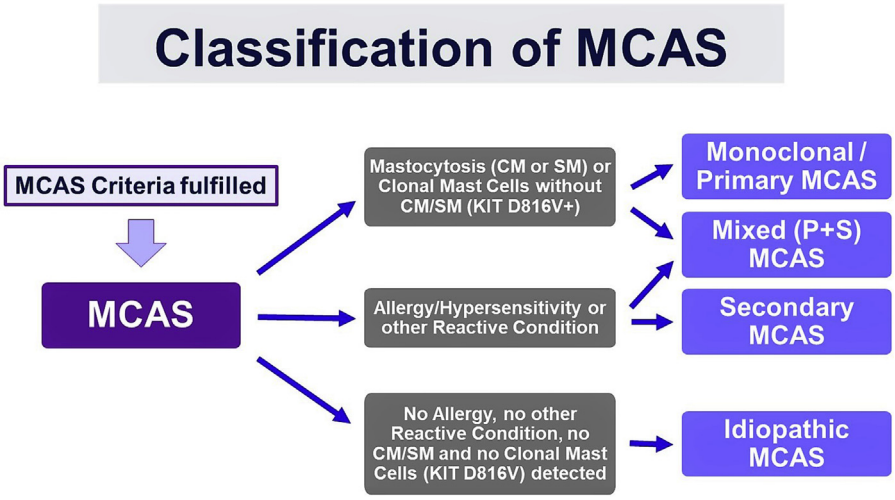

FIGURE 2. Classification of mast cell activation syndrome (MCAS). Once a diagnosis of MCAS has been established, it is classified into three variants based on the underlying disease or condition. Patients with MCAS can be divided into those with primary, secondary, and idiopathic MCAS. There are also patients who have a mixed MCAS variant exhibiting features of both primary and secondary MCAS. The terms "clonal MCAS" and "monoclonal MCAS" (monoclonal mast cell activation syndrome) can be used synonymously with the term "primary MCAS." Most patients with primary MCAS have cutaneous mastocytosis (CM) or systemic mastocytosis (SM). However, in some cases, criteria for SM and CM are not fulfilled, because only one or two minor SM criteria are detected (eg, *KIT* mutation at codon 816 and/or flow cytometry will detect an aberrant population of CD25-positive MCs). Secondary MCAS is usually diagnosed in patients with IgE-dependent allergies who experience food-, drug-, or Hymenoptera venom–induced anaphylaxis. Finally, severe MCAS can occur without a known or demonstrable etiology. These patients are classified as having idiopathic MCAS. *P*, primary; *S*, secondary.

such as vancomycin or narcotics interacting with MRGPRX2),[98] physical stimuli, exercise, stress, toxins, venoms, conditions leading to the activation of complement, and products of certain pathogenic microorganisms. Mast cell receptors involved in such reactions include receptors for C3a and C5a, cytokine receptors, MRGPRX2, viral receptors, and Toll-like receptors.

The most severe forms of MCA occur in combined forms of MCAS, in which several factors act together. For example, in patients with SM and MCAS, an IgE-dependent allergy may be documented. These patients may have a combination of primary and secondary MCAS (so-called mixed MCAS)[99]; thus, they are at high risk for developing recurrent life-threatening anaphylaxis, particularly after Hymenoptera stings,[23,100-102] but they might also be after exposure to food, drugs, and other allergens.[103-105] Mast cell activation syndrome patients with Hymenoptera venom–induced anaphylaxis who have concomitant mastocytosis (mixed MCAS) are usually offered lifelong venom immunotherapy.[106,107]

Finally, there are MCAS patients in whom no *KIT*-mutated MCs, no allergy, and no overt inflammatory disorders or triggers of a hypersensitivity reaction are detected. These patients have idiopathic MCAS.[28,30] In most lay literature, MCAS is incorrectly used identically with idiopathic MCAS. Idiopathic anaphylaxis (IA) is the prototype form of idiopathic MCAS; therefore, it is essential to evaluate whether the patient meets criteria for IA. However, the most important difference between idiopathic MCAS and IA is that the MCAS criteria are fulfilled in idiopathic MCAS patients, whereas in IA, proof of MC involvement (eg, acute tryptase elevation) is not required.

WHEN TO PERFORM A BM INVESTIGATION

Before a BM examination is considered, the initial screen should include a detailed physical examination with skin inspection, blood counts, and serum chemistry, including an sBT level, as well as peripheral blood testing for *KIT* D816V and HαT if the tests are available.[30] If *KIT* D816V is detectable in an adult patient, a BM examination is recommended regardless of the tryptase level and HαT status.[30,95,108,109] If *KIT* D816V mutation is not detected but HαT is found, BM investigations are not recommended, provided that no other features suggesting the presence of SM or another myeloid neoplasm are found. When all of these parameters show a negative result in a symptomatic patient, predictive tools such as the Spanish Network on Mastocytosis (Red Española de Mastocitosis [REMA]) score,[110] Karolinska score,[88] or National Institutes of Health Idiopathic Clonal Anaphylaxis Score[111] can be applied to estimate the likelihood that the patient has SM. This is particularly important in symptomatic patients who lack typical skin lesions.

DIFFERENTIAL DIAGNOSES

When patients do not present with typical symptoms of anaphylaxis or with chronic rather than episodic acute symptoms, it may be particularly challenging for a clinician to establish the correct diagnosis. This is because most symptoms attributable to MCA, such as isolated flushing, pruritus, headache, abdominal pain, or tachycardia, are not specific to MCs but can be found in other clinical conditions and disorders as well.[112-118] Hence, a broad range of differential diagnoses, including cardiovascular, endocrinologic, cutaneous, gastrointestinal, and neuropsychiatric disorders, should be

TABLE II. Overview of differential diagnoses mimicking mast cell activation and mast cell activation syndrome

Organ system	Disorder
Endocrine	Thyroid disease Adrenal insufficiency Hypopituitarism Estrogen or testosterone deficiency Carcinoid Pheochromocytoma Medullary thyroid tumor
Cutaneous	Hereditary or acquired angioedema Rosacea Idiopathic flushing Spontaneous/inducible urticaria Drug exanthema Atopic or contact dermatitis
Gastrointestinal	Inflammatory bowel disease Food intoxication (eg, scombroid fish poisoning) Irritable bowel syndrome Eosinophilic esophagitis or gastroenteritis Gastrointestinal motility disorders Vasoactive intestinal peptide-secreting tumor (VIPoma)
Cardiovascular	Arrythmias Myocardial infarction Endocarditis/endomyocarditis Aortic stenosis with syncope Pulmonary embolism
Neuropsychiatric	Seizures Stroke Multiple sclerosis Dysautonomia (eg, postural tachycardia syndrome) Vasovagal syncope Panic attacks and anxiety conditions Somatoform disorders
Immunologic	Vasculitis Systemic capillary leak syndrome Allergic episodes involving basophils but not mast cells Less severe conditions associated with mast cell activation
Infectious	Severe bacterial or viral infections ± septic shock Acute encephalitis/acute meningitis *Helicobacter pylori*-like-organism–positive gastritis with urticaria Acute gastrointestinal infection

considered in such patients[13,26,29,30,42,97,119] (Table II). Some of these patients may easily be given the incorrect diagnosis of having MCAS when applying less stringent criteria, but not the validated Vienna consensus criteria.[28,30] Although it is not a differential diagnosis, concurrent occurrence of hypermobile Ehlers-Danlos syndrome, postural orthostatic tachycardia syndrome, and MCAS was postulated. However, thus far, a definitive relationship among these conditions has not been demonstrated.

In general, MCAS is a syndrome defined by severe, recurrent, systemic reactions (usually in the form of anaphylaxis) that result from an acute and clinically significant release of vasoactive and proinflammatory MC mediators. When signs of anaphylaxis are not found, MCAS is much less likely to be the correct diagnosis. For less severe or localized forms of MCA (eg, limited to skin or respiratory tract) not fulfilling MCAS criteria, further research is needed to categorize these patients. Currently, there is no evidence to support the existence of a chronic form of MCAS without severe episodic events fulfilling MCAS consensus criteria. Patients with multiple chemical, environmental, or food intolerances should not be given the diagnosis of MCAS if they do not meet the Vienna consensus criteria.

HEREDITARY α-TRYPTASEMIA

Hereditary α-tryptasemia is an autosomal dominant genetic trait caused by increased *TPSAB1* copy number encoding α-tryptase; it may be accompanied by slightly increased numbers of MCs in BM and gastrointestinal biopsy specimens.[120-123] HαT is found in approximately 5% to 6% of the general population and results in elevated sBT levels typically greater than 8 ng/mL and often greater than 10 ng/mL.[121,124] Although only one study has examined the prevalence of symptoms among unselected individuals with HαT, up to two-thirds may have minimal or no symptoms. Initially, various clinical conditions, including dysautonomia with postural orthostatic hypotension, flushing, gastrointestinal hypomotility, joint hypermobility, vibratory urticaria, irritable bowel syndrome, chronic musculoskeletal pain, retained primary dentition, and allergic disorders, were reported in patients with HαT.[120,121,125-127] However, no consistent and definitive correlations among many of these phenotypes and HαT were established in subsequent studies. The frequency of HαT is the same in allergy patients compared with unselected controls.[124] In addition, patients with HαT do not have a hyperactive MC phenotype in vitro and do not have increased levels of urinary MC products unless these patients do also have SM. Moreover, the precise role(s) of enzymatically inactive α-protryptase remains unclear. A recent description of α/β-tryptase heterotetrameric tryptases, which have expanded biologic functions relative to mature β-tryptases, may offer a possible mechanism explaining MCA in these individuals.[128,129] It has also been reported that increased germline copies of *TPSAB1* are more prevalent among individuals with IA and SM. Further, HαT may be associated with an increased severity of anaphylactic reactions and other mediator-induced symptoms in patients with mastocytosis and venom allergy.[25,129]

The exact percentage of patients with clonal and idiopathic MCAS who concurrently have HαT is unknown. However, an approximately two to three times higher prevalence of HαT has been reported in two large cohorts of SM patients[25,129]; also, HαT concurrently occurring with MCAS has been reported.[130,131] Therefore, more research is warranted to understand the relationship between HαT and MCAS.

CURRENT CONTROVERSIES AND DIAGNOSTIC DILEMMA: OVERDIAGNOSING VERSUS UNDERDIAGNOSING

Some authors have based the diagnosis of MCAS on a variety of clinical symptoms that may or may not relate to MCA.[31,34] Many of these symptoms are caused by conditions involving other mechanisms or cells but not MCs. Some of these authors also question the necessity of why only severe, recurrent

symptoms should qualify as MCAS criteria, and instead conclude that many chronic symptoms may be attributable to MCAS. Accordingly, these authors apply the diagnosis of MCAS to many patients with diverse diseases and unresolved complex medical conditions.[31,132] Clinical criteria that these authors consider to be specific for MCAS include, but are not limited to, fatigue, pain, edema, dermographism, tinnitus, adenopathy, hypertension, endometriosis, polycystic ovarian syndrome, prostatitis, autoimmune disorders, solid organ malignancies, and various endocrinologic, gastroenterologic, neuropsychiatric, and hematologic disorders[31] (Figure 1). Considering the number of possible diseases in the differential diagnosis, which might account for the symptoms described, there is no scientific basis for assuming that any of these manifestations qualify as specific indicators of MCA or MCAS. When the diagnosis of MCAS is excluded by diagnostic consensus criteria, patients may well benefit by referral to appropriate specialists as determined by clinical and laboratory findings.

There is considerable concern regarding the consequences of overdiagnosing MCAS by using less stringent and less specific criteria.[31,34] For example, when including an elevation of mediators relatively specific for MCs, it is also important to define thresholds and especially the event-related further minimal threshold increase that could qualify for MCAS in such patients. We are of the opinion that patients with typical symptoms without confirmed event-related elevation of any validated biomarker of MCA should not be given a diagnosis of MCAS. An argument against using such markers is the limited access to these tests.[31] Furthermore, MCAS patients may chronically experience certain symptoms, so that a truly asymptomatic sBT is difficult to obtain.[31] Also, some authors have claimed that patients with MCAS had lower levels of serum tryptase during life-threatening anaphylaxis compared with baseline tryptase levels.[31] However, these arguments do not have a scientific basis and do not justify the use of less stringent criteria. Other authors have suggested employing the number of MCs in tissue sections (eg, $\geq$20 MCs per high-power field) as a criterion of MCAS.[31-33] However, many reactive inflammatory states and neoplasms, as well as individuals with no specific symptoms, may present with an increase in local MCs without MCA and without fulfilling criteria for MCAS.[133]

Overall, with a broader diagnostic approach and less stringent criteria.[31] there is a risk for overdiagnosing MCAS, especially with the use of non-validated, less specific (or nonspecific) laboratory tests. A resulting misdiagnosis of MCAS may affect patients by delaying appropriate medical management and consequently impairing their quality of life and prognosis.[134,135] In addition, the wrong diagnosis may lead to an inappropriate use of certain pharmacologic agents.[136]

FUTURE DIRECTIONS AND PROPOSED SOLUTIONS

In the recent past, increasing numbers of patients have been informed or believe that they have MCAS, without fulfilling diagnostic consensus criteria for MCAS. This is largely due to the publication of alternative, less stringent diagnostic criteria that are not robust and have not been validated in the context of MCAS. As a result, many patients are now given the diagnosis of MCAS without proved MC involvement or MCA. Similarly, it has also been recently suggested that MCAS is seen in a significant number of individuals who have experienced a COVID-19–associated illness. In this situation and in others in which Vienna consensus criteria are not met, the concern is that an underlying disease unrelated to MCAS may be present and the diagnosis of such an underlying condition may be delayed or missed.[119] We are also aware that there are individuals with chronic and local forms of MCA for whom MCAS criteria are not fulfilled. At present, however, solid diagnostic criteria for such conditions are lacking in such patients. We are of the opinion that patients with suspected MCAS must undergo an appropriate evaluation for symptoms or conditions according to evidence-based standards following Vienna consensus criteria, and that the diagnosis of MCAS should not be applied in the absence of findings required to fulfill Vienna consensus criteria for the diagnosis of MCAS. There is also hope that in the future, more MCAS-related biomarkers will be developed to support the physician in separating MCAS from MCAS mimickers.

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