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Clinical Commentary Review

Global Classification of Mast Cell Activation Disorders: An *ICD-10-CM*–Adjusted Proposal of the ECNM-AIM Consortium

Peter Valent, MD[a,b], Karin Hartmann, MD[c,d], Patrizia Bonadonna, MD[e], Theo Gülen, MD[f,g], Knut Brockow, MD[h], Ivan Alvarez-Twose, MD, PhD[i], Olivier Hermine, MD, PhD[j], Marek Niedoszytko, MD, PhD[k], Melody C. Carter, MD[l], Gregor Hoermann, MD, PhD[b,m], Joseph H. Butterfield, MD[n], Jonathan J. Lyons, MD[o], Wolfgang R. Sperr, MD[a,b], Georg Greiner, MD, PhD[b,p], Karl Sotlar, MD[q], Hanneke C. Kluin-Nelemans, MD, PhD[r], Juliana Schwaab, MD[s], Magdalena Lange, MD, PhD[t], Tracy I. George, MD[u], Frank Siebenhaar, MD[v,w], Sigurd Broesby-Olsen, MD[x], Mohamad Jawhar, MD[s], Boguslaw Nedoszytko, PhD[t,y], Mariana Castells, MD, PhD[z], Alberto Orfao, MD, PhD[aa], Jason Gotlib, MD, MS[bb], Andreas Reiter, MD[s], Hans-Peter Horny, MD[cc], Massimo Triggiani, MD, PhD[dd], Michel Arock, PharmD, PhD[ee], Dean D. Metcalfe, MD, MS[l], and Cem Akin, MD, PhD[ff] *Vienna and Salzburg, Austria; Basel, Switzerland; Verona and Salerno, Italy; Stockholm, Sweden; Munich, Mannheim, and Berlin, Germany; Toledo and Salamanca, Spain; Paris, France; Gdansk and Sopot, Poland; Bethesda, Md; Rochester, Minn; Groningen, The Netherlands; Salt Lake City, Utah; Odense, Denmark; Boston, Mass; Stanford, Calif; and Ann Arbor, Mich*

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Learning objectives:

1. To develop the ability to diagnose mast cell activation disorders (MCAD), including mast cell activation syndromes (MCAS) using diagnostic criteria and to distinguish between true MCAD/MCAS and MCAD/MCAS-like conditions.

2. To understand the mechanisms of mast cell activation and recognize the impact of underlying predisposing and triggering conditions and pathologies.

3. To acquire the ability to classify MCAS into MCAS variants, and to distinguish between MCAS, other MCAD, and unspecified MCAD where mast cell involvement is not always confirmed.

4. To develop management skills for patients with MCAD and MCAS, including prevention and prophylaxis, basic anti-mediator-type therapy, and special forms of intervention.

5. To understand the importance of multiple (and sometimes co-existing) predisposing and cooperating mast cell activation-inducing conditions and pathologies, recognize combined forms of MCAS, and develop skills to manage these combined and thus more severe MCAS patients by applying personalized medicine approaches.

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Mast cell activation (MCA) is common and occurs in a number of pathologic conditions, including IgE-dependent and independent allergic reactions, atopic disorders, autoimmune processes, and mastocytosis. In a subset of patients, no underlying disease and no known trigger of MCA are found. When the symptoms are severe, systemic, and recurrent, and accompanied by a diagnostic increase in the serum tryptase level or other mast cell mediators, an MCA syndrome (MCAS) may be diagnosed. In these patients, the symptoms typically respond to drugs suppressing MCA, mediator production in mast cells, or mediator effects. In each case, diagnostic consensus criteria must be fulfilled to diagnose MCAS. In other patients, MCA may be local, less severe, or less acute, or may be suspected but not confirmed, so that the diagnostic criteria of MCAS are not fulfilled. In these patients, it may be difficult to prove MCA, for example, by measuring multiple mast cell mediators or basophil activation, the latter as a surrogate of IgE-dependent hypersensitivity. However, validated diagnostic criteria for

[a]Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Vienna, Austria
[b]Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria
[c]Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland
[d]Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland
[e]Allergy Unit, Verona University Hospital, Verona, Italy
[f]Department of Respiratory Medicine and Allergy, Karolinska University Hospital Huddinge, Stockholm, Sweden
[g]Department of Medicine Solna, Division of Immunology and Allergy, Karolinska Institutet, Stockholm, Sweden
[h]Department of Dermatology and Allergy Biederstein, Technical University of Munich, Munich, Germany
[i]Instituto de Estudios de Mastocitosis de Castilla La Mancha (CLMast) and CIBERONC, Hospital Virgen del Valle, Toledo, Spain
[j]Service d'hématologie, Imagine Institute Université de Paris, Sorbonne, INSERM U1163, Centre national de référence des mastocytoses, Hôpital Necker, Assistance publiquehôpitaux de Paris, Paris, France
[k]Department of Allergology, Medical University of Gdansk, Gdansk, Poland
[l]Mast Cell Biology Section, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md
[m]MLL Munich Leukemia Laboratory, Munich, Germany
[n]Mayo Clinic, Division of Allergic Diseases, Rochester, Minn
[o]Translational Allergic Immunopathology Unit, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md
[p]Department of Laboratory Medicine, Medical University of Vienna, and Ihr Labor, Vienna, Austria
[q]Institute of Pathology, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria
[r]Department of Haematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[s]Department of Hematology and Oncology, University Hospital Mannheim, Mannheim, Germany
[t]Department of Dermatology, Venereology and Allergology, Medical University of Gdansk, Gdansk, Poland
[u]Department of Pathology, University of Utah, Salt Lake City, Utah
[v]Institute of Allergology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt - Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
[w]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany
[x]Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark
[y]Invicta Fertility and Reproductive Center, Molecular Laboratory, Sopot, Poland
[z]Division of Allergy and Immunology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass
[aa]Servicio Central de Citometria, Centro de Investigacion del Cancer (IBMCC; CSIC/USAL), Instituto Biosanitario de Salamanca (IBSAL), CIBERONC and Department of Medicine, University of Salamanca, Salamanca, Spain
[bb]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, Calif
[cc]Institute of Pathology, Ludwig-Maximilians-University, Munich, Germany
[dd]Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy
[ee]Department of Hematological Biology, Pitié-Salpêtrière Hospital, Pierre et Marie Curie University (UPMC), Paris, France
[ff]Division of Allergy and Clinical Immunology, University of Michigan, Ann Arbor, Mich

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Corresponding author: Peter Valent, MD, Department of Internal Medicine, Division of Hematology and Hemostaseology and Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Waehringer Guertel 18-20 Vienna, Austria. E-mail: peter.valent@meduniwien.ac.at.

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Abbreviations used
HαT- hereditary alpha tryptasemia
ICD-10-CM- International Classification of Diseases, Tenth Revision, Clinical Modification
MC- mast cell
MCA- MC activation
MCAD- MCA disorder
MCAS- MCA syndrome
PGD_2- prostaglandin D_2
SM- systemic mastocytosis

implicating suspected MCA behind such conditions are lacking, even if some of these conditions have recently been assigned to an *International Classification of Diseases-10-Clinical Modification* code (*ICD-10-CM*). In this article, we discuss diagnostic features and criteria and propose a *ICD-10-CM*–adjusted classification for disorders associated with MCA, herein referred to as MCA disorders (MCADs), with special emphasis on the delineation between confirmed MCAS, MCAD not fulfilling MCAS criteria, and suspected MCAD that is not present. In addition, we discuss the discrimination between overt MCAD and predisposing conditions, such as atopic states, mastocytosis, and hereditary alpha tryptasemia. **(J Allergy Clin Immunol Pract 2022;10:1941-50)**

Key words: *Mastocytosis; Mast cell activation; HαT; Diagnostic criteria; MCAS*

INTRODUCTION

Mast cells (MCs) are key effector cells in IgE-dependent allergic disorders and other inflammatory conditions.[1-6] MCs exhibit high-affinity receptors for IgE (IgER = FcεRI) and produce inflammatory and vasoactive mediators, including histamine, tryptases, other proteases, prostaglandin D_2 (PGD_2), cysteinyl leukotrienes, and diverse chemokines and cytokines.[1-6] In physiologic states, several of these molecules are stored in the secretory granules of MCs. Some of these mediators, such as alpha tryptase, are released from MCs at a constant low rate under physiologic conditions, resulting in a low baseline serum concentration.[5,7,8] During an anaphylactic episode, cross-linking of FcεRI is followed by a massive and rapid release of granular mediators and enzymes from MCs.[2-6] In addition, during degranulation, cell surface and cytoplasmic membranes of MCs are rearranged, and lipid membrane–derived mediators are produced and secreted.[2-6] Basophils behave in a similar manner and can thus also contribute to allergic and other inflammatory reactions.[9,10] However, in severe anaphylaxis, MCs are generally considered to be the primary cell involved in the resulting pathology.

The capacity of MCs to release mediators of anaphylaxis in response to a specific trigger (agonist) depends on various circumstances and factors, including the genetic background of the patient, underlying pathology (disease), and the numbers and types of receptors and signaling molecules involved.[11-15] The severity of an anaphylactic reaction is further determined by the numbers of MCs involved, cytokine exposure, the nature and number of triggers and cofactors (eg, IgE-reactive allergens, nonsteroidals, and toxins such as those within venoms), the type and amount of IgE, the presence of comorbidities (eg, allergy, infectious diseases, or mastocytosis), epigenetic factors, and other patient-related variables (cardiovascular status, physical exercise, nutrition, alcohol, drugs).[3,11-20]

MC activation (MCA) occurs in a number of physiologic and pathologic states. Acute MCA accompanies IgE-dependent allergic reactions and may result in the clinical picture of anaphylaxis.[2,3,11-14,19] Severe or even life-threatening MCA may develop when (1) the burden of MCs is high, and/or (2) when most or all MCs are in a "hyperactivated" state and release all their mediators massively and instantly, and/or (3) when comorbidities such as cardiovascular or pulmonary diseases contribute substantially to an MCA event. When hypersensitivity reactions are severe, systemic, and recurrent, an MCA syndrome (MCAS) may be diagnosed.[21-26] Although in most of these patients, anaphylaxis is diagnosed, there are also patients who suffer from MCAS and fulfill all MCAS criteria, but do not necessarily exhibit the classical clinical features of anaphylaxis.

In the past 10 years, diagnostic criteria and a classification for MCAS have been established by an international (European Union/US-based) consensus group.[21,22,24] In addition, a diagnostic algorithm for MCAS has been developed.[26] However, there is still debate about the use of the term MCAS in various groups of patients, and many questions remain. For example, many patients with suspected MCAS and signs of MCA do not fulfill MCAS criteria.[27-29] In these patients, MCA may be suspected as the major clinical problem, but it is a significant challenge to prove with certainty that the clinical features and symptoms are indeed derived from MC-dependent reactions and mediator release. Some of these patients have MCA disorders (MCADs) or nonspecified MCA reactions or suspected MCA.[27-29] In these patients, local MCA, less severe MCA, or MCA potentially involving only a limited set of mediators or only 1 organ system may be implicated, whereas other patients do not have an MCAD.

More recently, *International Classification of Diseases-10-Clinical Modification* (*ICD-10-CM*) codes have been created in the United States for most of these conditions, but there are no features or criteria through which these conditions can be diagnosed with certainty, leaving the possibility of overdiagnosis of MCA, which may lead to inappropriate patient management. To address this unmet need, our consensus group has worked out a proposal for disease-related clinical features and laboratory-based results that may qualify as indication of MCA and may even serve as criteria of MCAD not meeting MCAS criteria. In addition, we propose a global classification of MCA-related conditions, including predisposing conditions and clinically overt MCAD that can further be divided into (1) confirmed MCAS (and MCAS variants) and (2) other MCADs not fulfilling (all) diagnostic criteria to establish an MCAS, in contrast to cases of suspected MCAS/MCAD that are ruled out by history and/or laboratory evaluation.[28]

DIAGNOSTIC CRITERIA AND CLASSIFICATION OF MCAS

The diagnosis of MCAS is suspected when (1) clinical symptoms are severe, (2) systemic, involving at least 2 organ

systems, and (3) recurrent, most commonly in the form of repeated anaphylaxis, and (4) evidence of involvement of MCs is demonstrable.[21,22,24-29] Based on consensus criteria (Table I), the diagnosis of MCAS can be established when (a) typical clinical symptoms arising from recurrent acute systemic (multiorgan) MCA (typically in the form of recurrent anaphylaxis) have been documented, (b) MC-derived mediators increase substantially in serum or urine over the individual's baseline (standard marker: documented increase in serum tryptase levels following the 120% + 2 ng/mL formula; eg, increase in serum tryptase from a basal level of 50 to 70: 50 + 10 [20%] = 60 + 2 = 62: any value beyond 62 counts as biochemical MCAS criterion), and (c) the symptoms respond to drugs blocking MCA, MC mediators, mediator production, or mediator effects.[21,24-28] All 3 criteria must be fulfilled to conclude that the patient is suffering from MCAS (Table I). When the tryptase test is not available or the result is inconclusive, other biomarkers indicative of MCA, such as an increase in histamine metabolites or PGD_2 metabolites in urinary samples (spot urine taken within a few hours after an event or over a 24-hour period after an event) to more than 200% (+100%) of the individual's baseline (measured in a symptom-free interval) in association with an event, may be used as alternative diagnostic marker, although this minimal diagnostic threshold has not yet been validated (Table I).[26]

When the diagnosis of MCAS has been established, the next essential step is to determine the etiology and to classify MCAS.[21,24-26] Based on the underlying condition(s), MCAS can be split into (a) monoclonal (= clonal or primary) MCAS, where *KIT*-mutated, monoclonal (often $CD25^+$) MCs are detected and an underlying mastocytosis is often found, (b) secondary MCAS, where an underlying nonneoplastic disease, usually an IgE-dependent allergy, is detected, and (c) idiopathic MCAS, where no underlying disease and no MC clonality that could explain MCA is found (Table II).[21,24-26] Monoclonal MCAS may also develop in patients with *KIT*-mutated (usually *KIT* $D816V^+$) MCs in whom the diagnostic criteria for mastocytosis are not all fulfilled.[21,24-26,30,31] In some of these patients, overt systemic mastocytosis (SM) may develop during follow-up.

In a substantial number of cases, monoclonal (primary) as well as secondary MCAS may be diagnosed, for example, in patients with SM who also suffer from an IgE-dependent allergic disease. We propose that this constellation be termed combined (mixed) MCAS. These patients are at a high risk to develop life-threatening anaphylaxis and therefore need special attention and individualized therapeutic approaches (Table II).[32-37] For example, in patients with SM and an IgE-dependent allergy against insect (bee or wasp) venom, the risk to develop recurrent life-threatening anaphylaxis after a bee or wasp sting is very high.[32-37] These patients are candidates for life-long immunotherapy and in selected cases can also be considered to be candidates for IgE-targeting antibody therapy (eg, omalizumab) with the aim of preventing severe MCAS events.[37-45] Detailed knowledge about the etiology and the complexity of MCAS is thus critical and forms an important basis for establishing the exact diagnosis and for developing an optimal treatment plan.

An important associated question is whether patients with hereditary alpha tryptasemia (HαT) and documented MCAS should be classified as suffering from primary MCAS, secondary MCAS, or as idiopathic MCAS when no other underlying etiology or disease is detected. Because HαT is not a clonal disease but rather a genetic trait, and the exact relationship between HαT and anaphylaxis remains unclear, this question remains open. One approach would be to call this condition HαT-associated (HαT+) MCAS (Table II).

Another important question is whether patients who are treated at the intensive care or emergency unit because of clinically diagnosed anaphylactic shock can be classified as suffering from MCAS if no serum tryptase level is available and/or these patients do not immediately respond to anti−mediator-type therapy. The recommendation is that these patients be initially diagnosed with anaphylaxis, and only later diagnosed and classified as patients with MCAS when all MCAS criteria are fulfilled.

TABLE I. Diagnostic consensus criteria for MCAS*

A. Typical clinical signs of severe, recurrent (episodic) systemic MCA are present (often in the form of anaphylaxis) (definition of systemic: involving at least 2 organ systems)
B. Involvement of MCs is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual's baseline to 120% + 2 ng/mL†
C. Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production, or drugs blocking mediator release or the effects of MC-derived mediators‡

*All 3 MCAS criteria (A + B + C) must be fulfilled to call a condition MCAS.
†Other MC-derived biomarkers of MC activation (recommended: 24-h or spot urinary histamine metabolites or PGD_2 metabolites) may also be used, but are less specific compared with the increase in serum tryptase level. In addition, to date, no diagnostic thresholds for the increase in these urinary biomarkers have been defined and validated. Nevertheless, these alternative markers are recommended when the tryptase test is not available or its result is inconclusive. A proposed diagnostic threshold for histamine or PGD2 metabolites is >200% of the individual's baseline (increase by >+100%) provided that the test result is above the normal range for the assay.
‡Example: histamine receptor blockers.

PREDISPOSING CONDITIONS AND PATHOLOGIES THAT MAY CONTRIBUTE TO THE ETIOLOGY AND MANIFESTATION OF MCAS AND OTHER MCADs

A number of underlying pathologies, predisposing genetic conditions, and comorbidities have been identified as potential triggers of MCA and thus cofactors relevant to the manifestation of MCAS and other MCADs (Table III). As outlined before, IgE-dependent allergies and clonal MC disorders (mastocytosis) are considered major underlying conditions and triggers of MCAS, especially when both conditions are present in the same patient.[32-37,44] There are also IgE-independent (eg, IgG-dependent or complement-dependent or MRGPRX-2 receptor−mediated) hypersensitivity reactions, other atopic disease states (atopic diathesis), or physical stimuli such as exercise, vibration, or temperature that may contribute to the manifestation of an MCAS.[3,46] Local inflammatory reactions and (viral or bacterial) infections may also induce or aggravate anaphylactic reactions and so that an MCAS or other MCAD is diagnosed.

In SM, the lifetime risk of anaphylaxis has been reported to be 30% to 40%. Patients with SM have a high risk to develop severe mediator-related symptoms and MCAS for several reasons.[33-37,44] First, the numbers of the cells involved (MCs) can greatly increase in patients with SM. Second, MCs in SM are presumed to be in an activated state, especially when these patients are also carriers of HαT and/or suffer from an allergic disease.[33-37,44] Finally, the *KIT* D816V mutation has been implicated in

TABLE II. Recognized variants of MCASs and estimated risk for development of life-threatening anaphylactic MCAS events

Variant of MCAS	Main diagnostic features	Estimated risk for repeated severe anaphylaxis
Monoclonal MCAS = clonal MCAS* = primary MCAS*	The *KIT* D816V mutation is detected and MCs may display CD25 and/or CD30 (a) with confirmed mastocytosis (CM or SM)† (b) only 2 minor SM criteria are met†	++
Secondary MCAS	An IgE-mediated allergy, another hypersensitivity reaction, or another immunologic disease that can induce MCA and thus MCAS is diagnosed, but no neoplastic MCs or *KIT* D816V is found‡	++
Combined MCAS	Criteria for primary MCAS and secondary MCAS are fulfilled, and HαT may also be detected§	+++
HαT^{+} MCAS	HαT is detected and all diagnostic MCAS criteria are fulfilled	+/++
Idiopathic MCAS	Criteria to diagnose MCAS are met, but no related reactive disease, no IgE-dependent allergy, and no neoplastic/clonal MCs are detected; in addition,‖ no HαT is known or found	+

CM, Cutaneous mastocytosis.
Risk score: +, low risk; ++, high risk; +++, exceptionally high risk.
*The terms monoclonal MCAS (also known as MMAS) and clonal MCAS are used synonymously with the term primary MCAS.
†Most of the patients suffer from SM. However, in some cases, only 2 minor SM criteria are detected and criteria for SM and CM are not fulfilled.
‡Apart from IgE-dependent mechanisms, a number of other underlying pathways and mechanisms (IgG-mediated, complement-mediated, and MRGPRX2-mediated) reportedly may lead to a massive MCA and thus MCAS.
§Patients with a combined HαT + MCAS may have the highest risk to develop recurrent severe (life-threatening) anaphylaxis.
‖No *KIT* mutation at codon 816 is detected, and flow cytometry (if performed) will not detect a clonal population of CD25-positive MCs.

TABLE III. Conditions and comorbidities predisposing to the development of anaphylaxis and MCAS or other MCADs, and potentially underlying or known mechanisms

Condition/disease	Potential underlying mechanism(s)
Genetic/hereditary	
HαT	Increased sensitivity to certain triggers (eg, α/β-tryptase–induced cleavage of mechanosensory receptors, leading to vibration-triggered degranulation of MCs) Increased numbers of tissue MCs
Atopic diathesis	Increased tissue inflammation triggered by autoallergens and related exogenous allergens through multiple mechanisms
Predisposing comorbidities	
Hypersensitivity disorders	
IgE-dependent allergies	IgE-dependent activation of MCs
IgE-independent hypersensitivity	MC activation by other triggers, such as IgG, or complement components
Atopic disorders with chronic tissue inflammation	IgE-dependent activation of MCs and cytokine/chemokine-induced activation of MCs in various tissues and organs, such as the skin or the lung
Cutaneous Mastocytosis (CM)	Increased MC burden in the skin
Systemic Mastocytosis (SM)	Increased MC burden in internal organs (bone marrow, spleen, and others), with or without skin involvement
Other disorders potentially involving MC	
Autoimmune disorders involving MCs	Chronic activation of MCs in inflamed tissues (IgE-, IgG-, or complement-mediated)*
Chronic inflammatory diseases involving MCs	Chronic activation of MCs in inflamed tissues (complement- or cytokine-mediated)*
Infectious diseases involving MCs	MC recruitment and activation induced by certain microbes and their products*

*Typical examples with evidence of MC involvement in reactive conditions or inflammatory disorders (including chronic and/or autoimmune and infectious disorders) are bullous pemphigoid, acute graft-versus-host disease, rheumatoid arthritis, viral infections, and chronic helminth infections.

MCA, because KIT activation by its ligand, stem cell factor, can also trigger MCA and sensitize MCs against IgE-dependent stimuli.[16,17] Indeed, activating mutations in the *KIT* gene are commonly detected in patients with SM.[47] However, expression of *KIT* D816V in MC lines does not necessarily lead to increased releasability.[48] Rather, in some experimental models, *KIT* D816V even seems to downregulate MCA.[48] Correspondingly, many patients with SM do not suffer from any MCA-related events, even if the burden of MCs is high. In addition, there are patients with SM who suffer from repeated episodes of severe anaphylaxis and MCAS despite a low burden of neoplastic MCs.[34-37] In other words, the severity of MCAS events does not necessarily correlate with the burden of MC or tryptase levels in patients with SM but may depend on other features (variables)

TABLE IV. MCA-related disorders (MCADs), predisposing conditions, and official *ICD-10-CM* codes

Disorder/condition	Abbreviation	*ICD-10-CM* code
MCA-related disorders (MCADs)		
Mast cell activation (disorder), unspecified*	MCA(D)-NOS*	D89.40*
Mast cell activation (syndrome)	MCA(S)	D89.40
Monoclonal MCAS	MCAS-m	D89.41
Idiopathic MCAS	MCAS-i	D89.42
Secondary/reactive MCAS	MCAS-s/r	D89.43
Other mast cell activation disorder(s)*	MCAD	D89.49*
Conditions predisposing to MCA/MCAD		
Hereditary alpha tryptasemia	HαT	D89.44
Atopic diathesis	Various	Various
Hypersensitivity disorders	Various	Various
IgE-dependent allergies	Various	Various
IgE-independent hypersensitivity	Various	Various
Intolerance syndromes	Various	Various
Toxin exposure (poisoning)	Various	Various
Cutaneous mastocytosis	CM	D47.01
Childhood-onset cutaneous mastocytosis	CM	Q82.20
Bone marrow mastocytosis	BMM	D47.02
Indolent systemic mastocytosis	ISM	D47.02
Smoldering systemic mastocytosis	SSM	D47.02
Aggressive systemic mastocytosis	ASM	C96.21
Systemic mastocytosis with an associated hematologic neoplasm	SM-AHN	D47.02 + code for AHN
Mast cell leukemia	MCL	C94.30
Mast cell sarcoma	MCS	C96.22
Mastocytoma (of skin)	—	D47.09

*For these conditions, no validated criteria are available to date; an initial attempt and proposal to define features and criteria in these conditions is presented in Table V. However, it should be mentioned that these criteria should not be used in a global manner to replace MCAS as a diagnosis when MCAS criteria are not fulfilled. Rather, in such individuals, alternative diagnoses and etiologies must be considered.

such as the MC maturation stage and/or expression levels of IgE receptors on MCs.[3,14,19,49] Finally, any type of mastocytosis, including variants of cutaneous mastocytosis and variants of SM, can predispose to the development of an MCAS, localized MCA (often in the skin), or another MCAD (Tables III and IV).

More recently, HαT has been described as a new genetic condition (germline trait) and reported in some cohorts to be associated with a higher risk of severe mediator-related symptoms in Hymenoptera-allergic individuals and patients with SM.[15,50-55] Moreover, the HαT carrier status is more prevalent in patients with SM (15%-20%) compared with the general (otherwise healthy) population (around 5%).[15,54] In most individuals with HαT, the serum tryptase level is slightly to markedly elevated, but may in some HαT carriers be within normal range.[15,50-56] In those HαT carriers who are also suffering from SM, the serum tryptase levels are usually higher than one would expect from the burden of neoplastic MCs detected by histology in the bone marrow.[54] Whether HαT per se can cause MCA or even MCAS (in the absence of an allergy and/or mastocytosis) remains uncertain. HαT carriers do not have increased levels of other MC mediators, and MCs carrying the HαT genotype do not appear to be more sensitive to specific IgE-mediated degranulation *in vitro*.[50] Moreover, most HαT carriers are asymptomatic or suffer only from mild mediator-induced symptoms, so that based on existing information, we are of the opinion that HαT per se, although recently assigned to an *ICD-10-CM* code (D89.44), is not likely a complete trigger of MCA or an independent inducer of MCAD/MCAS events.[15,50-56]

Table III presents a summary of underlying pathologies, comorbidities, and conditions predisposing to MCAS and other MCADs, and Table IV presents a compilation of pathologies and conditions together with the related *ICD-10-CM* codes.

Other MCADs: What if MCA is suspected or documented but MCAS criteria are not met?

In some patients with suspected mediator-induced symptoms or symptoms that may resemble MCAS, the full spectrum of MCAS criteria cannot be documented at first presentation although involvement of MCs in disease pathogenesis appears obvious. For these cases, the provisional diagnosis "probable MCAS" may be appropriate. This diagnosis may then change in follow-up. For example, if a patient with clinical symptoms of MCAS and a diagnostic increase in tryptase did not respond to first-line therapy such as antihistamines but did respond to second-line therapy such as an anti-IgE antibody, the initial diagnosis would be "probable MCAS" and would change to MCAS when a response to second-line therapy has been documented.

In other patients (eg, with clinically diagnosed idiopathic anaphylaxis), symptoms are typical (=systemic and severe and recurrent) and an increase in the serum tryptase level (or other MC mediators) during an attack can be documented, but the elevation does not meet the 120% + 2 ng/mL threshold. In these patients, the term "MCAD" or "other MCAD" may be appropriate (*ICD-10-CM* code D89.49) (Table IV).[29] These patients should be managed and treated in the same way as those with MCAS. In fact, these patients usually respond to drugs targeting MCA, MC mediators, or mediator effects in the same way as patients with MCAS. It is also appropriate to ask for other MC mediators in these patients. Some of these patients can be reclassified as suffering from MCAS when tryptase and/or other MC-related mediators increase substantially during an attack in a subsequent investigation.[57-60] In some of the patients, the levels of urinary PGD_2 metabolites may increase substantially but serum tryptase levels increase only slightly. These patients may be classified as suffering from MCAS or other MCAD, depending on the symptomatology and the degree to which the MC mediators increase over the individual's baseline. For example, a patient with a massive increase in urinary histamine metabolite and/or PGD_2 metabolite (>+100% = >200% of the individual's baseline and above normal range for the assay) and some event-related increase in serum tryptase could be classified as suffering from MCAS. The

TABLE V. Diagnostic features of MCA-related disorders (MCADs) that do not fulfill MCAS criteria

MCAD	*ICD-10-CM* code	Proposed diagnostic features
MCA/MCAD unspecified* (MCAD NOS)	D89.40	A. Clinical and lab-based signs and symptoms of MCA in 1 or more organs, MC involvement not reconfirmed with certainty, symptoms may be chronic, less severe, and recurrent, and often involve only 1 organ system* B. Patients may or may not respond to drugs targeting MCs or MC mediators C. MCAS criteria are not fulfilled D. Often inappropriate to explain multisystem symptoms and should not be used as a primary or final diagnosis
Other MCAD*	D89.49	A. Typical clinical symptoms (MCAS-like) affecting 1 or more organ systems (with or without signs of anaphylaxis) B. Event-related increase in an MC-specific mediator (substantial increase in serum tryptase but below the MCAS threshold) or substantial increase in urinary histamine metabolite or PGD_2 metabolite† C. Response of symptoms to drugs targeting MCA, MC mediators, or mediator effects (mediator receptors) D. Criteria to diagnose MCAS are not completely fulfilled (sometimes 1 or 2 of the 3 mandatory MCAS criteria are met)‡ E. Often inappropriate to explain multisystem symptoms and should not be used as a primary or final diagnosis

NOS, Not otherwise specified.

*No robust validated diagnostic criteria are available for these conditions to date. Unspecified or "not otherwise specified (NOS)" means that involvement of the MC lineage in the signs and symptoms detected cannot be confirmed with certainty. In some of these patients, other cell types (basophils, eosinophils) may be more relevant as disease-triggering cell type than MCs.

†An increase in histamine metabolite or PGD_2 metabolite by at least 50% over the individual's baseline (total >150% of baseline and value must be above the normal range for the assay) should qualify as an indication (criterion) of an MCAD (other MCAD).

‡In these patients (2 of 3 MCAS criteria met), the provisional diagnosis "probably MCAS" may sometimes also be justified. For example, if a patient with clinical symptoms of MCAS and a diagnostic increase in tryptase would not respond to first-line therapy but would respond to second-line therapy, the initial diagnosis could be "other MCAD" or better "probably MCAS" and would change to definitive MCAS at the time when a response to therapy has been documented.

minimal diagnostic threshold increase in urinary histamine metabolite or PGD_2 metabolite for an (other) MCAD should be 50% over the individual's baseline (>150% total). The proposed thresholds for these urinary biomarkers of MCA are based on limited available data, and clinical validation studies are thus needed to support their clinical value in daily practice. Clinical features and criteria proposed for the group of patients suffering from "other MCADs" not fulfilling MCAS criteria (*ICD-10-CM* code D89.49) are presented in Table V.

In other patients, the clinical symptoms of MCA are less clear and there is only indication of a local or systemic reaction that presents some features of MCA but would not qualify as MCAS criteria.[26-29] For example, such patients may exhibit urticaria, with findings thus compatible with local MCA. In other patients, symptoms may be mild and involve only 1 organ, or are not typical for MCA and MCAS. Examples are isolated gastrointestinal symptoms (cramping, diarrhea, constipation, food intolerance), isolated skin symptoms (flushing, pruritus, edema, nondescript rash), or isolated neurological or psychiatric symptoms (headache, fatigue, brain fog, depression, seizures, focal neurologic deficits, psychosis). In most such instances, serum tryptase levels and other MC-derived mediators do not increase substantially (diagnostic increase over the individual's baseline not reached) during a symptomatic event. Some of these patients may also have typical signs and symptoms indicative of a localized MCA and related comorbidities, such as an IgE-mediated rhinoconjunctivitis or atopic dermatitis, which are common in the general population. In these patients, the term "MCAD unspecified" is not justified. For atopic symptoms, we recommend using *ICD-10-CM* codes specific for the atopic entity and not using the term "MCAD unspecified" as an overarching diagnosis. In particular, the certainty that MCs are indeed responsible for the reported symptoms in such a patient remains questionable (unconfirmed). Thus, an "unspecified MCA/MCAD" should not be considered a final diagnosis but should prompt the physician to search for additional (more definitive) indications (criteria) of MCA and for diseases in the differential diagnosis.[26-29] Indeed, an "unspecified MCA/MCAD" may turn out not to be MCA/MCAD in more detailed investigations. The designated *ICD-10-CM* code for cases of unspecified (unconfirmed) MCA/MCAD is D89.40 (Table IV). Diagnostic clinical features (potential diagnostic criteria) proposed for these patients are presented in Table V. It should be noted that it is usually impossible to establish a definitive relationship between the symptomatology and involvement of MCs in such patients. Therefore, we are of the opinion that the *ICD-10-CM* code for this condition should change to provide a contrast to MCAS, which, for the moment, has the same code as "MCA/MCAD, unspecified" (D89.40) (Table IV). All in all, the definitions and criteria we propose herein provide a scientific basis for addressing the existing *ICD-10-CM* codes relating to MC involvement in pathologic states and create a common language of criteria to be used for diagnostic subsets of patients to avoid misunderstanding and misdiagnoses. However, we also note that although this proposal is an important first step toward a unifying classification of MCAD (including MCAS), the *ICD-10-CM* codification and the definitions and classification of MCAD will need adaptations in the future based on new insights and more new specific markers of activation of MCs and other cell types.

PROPOSED GLOBAL CLASSIFICATION OF MCAD AND PREDISPOSING CONDITIONS

A proposed global classification of MCADs and of predisposing conditions is presented in Table IV. In this classification, MCAD, which represents the unifying umbrella term of all MCA-related conditions, is essentially divided into MCASs, other MCADs,

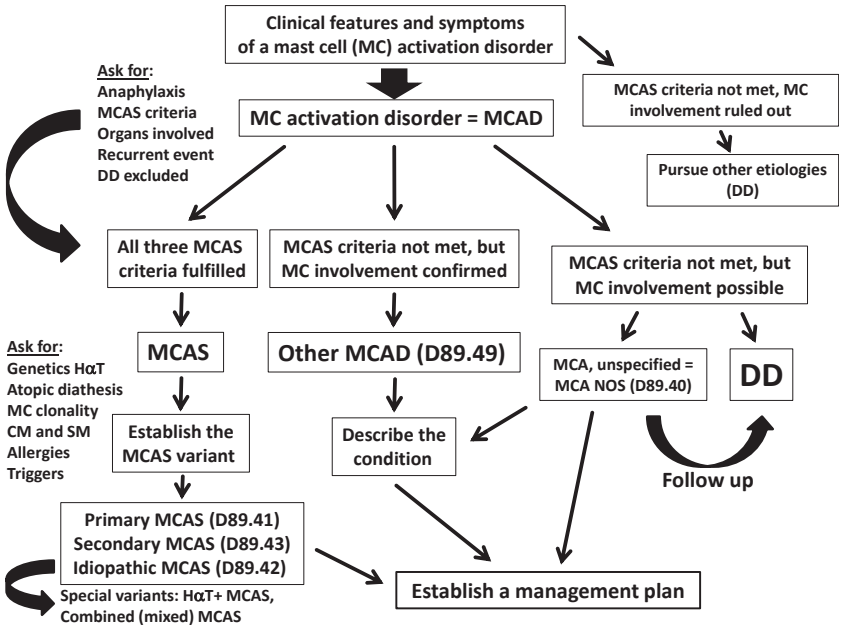

FIGURE 1. Proposed diagnostic algorithm for patients with suspected MCADs and MCASs. Not uncommonly, patients may suspect or have been labeled as having MCAS but have symptoms without clear relation to MCA and do not fulfill MCAS criteria; other etiologies (differential diagnoses [DD]) are important to explore in these patients. In patients with typical clinical features and symptoms of MCA, the physician will establish the provisional diagnosis of an MCAD. In addition, the physician will consider signs and symptoms of anaphylaxis, criteria of MCAS, and potential DD. MCAS is diagnosed when all 3 MCAS criteria are fulfilled: (1) typical (MCA-related) clinical symptoms; (2) an event-related increase in serum tryptase level; and (3) response to medications directed against MCA or effects of MC mediators. At that time, the physician will ask for the underlying etiology, contributing conditions (comorbidities), and potential triggers of MCA, and based on this information, a subtype (variant) of MCAS (defined by the consensus classification and the *ICD-10-CM* code) may be diagnosed. When MCAS criteria are not met but signs of MC involvement and MC activation are demonstrable (see Table V), the diagnosis "other MCAD" (*ICD-10-CM* code D89.49) may be present; however, this should not be used as a primary or final diagnosis to explain multisystem symptoms. In these patients, the condition should be described in sufficient detail, and triggering factors and underlying etiologies (including DD) should be explored. When MCAS criteria are not fulfilled but MC involvement is possible, the (provisional) diagnosis MC activation, unspecified or MCAD unspecified (MCAD, NOS) (*ICD-10-CM* code D89.40) may be present, but this also should not be accepted as a primary or final diagnosis to explain multisystem symptoms. In these cases, it is usually difficult or impossible to define the impact of MCs, and in many cases, an in-depth analysis of markers and symptoms in the follow-up will reveal the presence of an unrelated disease. Therefore, it is of crucial importance to search for DDs in these cases. Finally, in all groups of patients, a management plan should be established. *NOS*, Not otherwise specified.

and unspecified MCA (MCAD, unspecified or not further specified = NOS). MCASs in turn are split into several variants depending on the underlying (known) etiology (Table II). Although in all MCAS variants, all 3 MCAS consensus criteria must be fulfilled, this is not the case in other MCADs and in cases with unspecified MCA/MCAD (Tables II and V).[21-29] In "other MCAD," definitive signs and symptoms of MCA and thus evidence of MC involvement have been documented (Table V). In contrast, in patients with unspecified MCAD (MCAD, NOS), MC involvement may be suspected, but an MC disorder is not present (Table V). The proposed global classification of MCAD is in line with a proposed refined classification of all MC disorders recently published by our consensus group.[29]

PROPOSED DIAGNOSTIC ALGORITHM FOR PATIENTS WITH SUSPECTED MCAD

Figure 1 provides a diagnostic algorithm for patients with suspected MCAD and a related classification of MCADs. In this classification, MCAD serves as an umbrella term for all conditions (possibly or definitively) related to MCA, and all these conditions are labeled with the term MCAD or MCAS (MCAS being a special form of MCAD). In patients with typical clinical features and symptoms of MCA, a provisional diagnosis of an MCAD will be established (Figure 1). In addition, the physician will ask for signs and symptoms of anaphylaxis, criteria of MCAS, and potential differential diagnoses. The presence (or clinical suspicion) of anaphylaxis increases the likelihood that the patient is suffering from MCAS. When all 3 MCAS criteria are fulfilled (Table I), the diagnosis of MCAS can be established. At the same time (first referral) or shortly thereafter, the physician will also ask for the underlying etiology, contributing conditions (comorbidities), and potential triggers of MCA (Table II). Based on this information, the MCAS variant defined by the consensus classification (and *ICD-10-CM* code) will be established (Figure 1). As presented in Table IV, the diagnosis "other MCAD" (*ICD-10 CM* code D89.49) entails a suspected MC disorder in which criteria to diagnose MCAS (as presented in Table I) are not completely fulfilled. In such patients, presence of an MC disorder is not corroborated with certainty; this diagnosis

should not be used routinely in patients with multisystem symptoms and a lack of confirmatory criteria.[28] The diagnosis "MCA/MCAD, unspecified," = MCAD, NOS (*ICD-10-CM* code D89.40) entails a suspected MC disorder, but with no evidence of MC involvement based on clinical signs or symptoms or documented via laboratory evaluation. Such patients do not exhibit a salutary response to drugs targeting MCs or MC mediators. In these patients, MCAS criteria are not fulfilled, and presence of an MC disorder is not confirmed.[28] It is of utmost importance to search for differential diagnoses for cases in which MCAS is suspected but MCAS criteria are not completely fulfilled (Figure 1).

DIFFERENTIAL DIAGNOSES TO MCAD AND MCAS

There are a number of differential diagnoses to consider when examining a patient with suspected MCAS.[3,21-28] These are often disorders that can mimic various symptoms of anaphylaxis with severe hypotension.[3,21-28] Differential diagnoses include, among others, cardiovascular disorders, dehydration, septicemia, acute bleeding, intoxications, dysautonomia, anxiety and somatoform disorders, and psychiatric conditions. In contrast, differential diagnoses to "other MCAD" or "unspecified MCA/MCAD" are many more because the spectrum of symptoms is much broader (because symptoms are less severe, less specific, and often local and/or not confirmed). In fact, in these patients, differential diagnoses include, among others, skin diseases presenting with urticarial lesions, gastrointestinal disorders, food intolerances or aversions, chronic inflammatory (rheumatic) disorders, acute or chronic infections, endocrinologic diseases, joint diseases, intoxication, neurologic diseases, poisoning, drug side effects, psychological and psychiatric conditions, and more.[26,28] Alternative diagnostic criteria for MCAS have also been proposed,[61] but these criteria are much broader, less specific, and lack validation. Overdiagnosis of MCAS entails the risk for an underlying disorder unrelated to MCAS being present and a delay in establishing this diagnosis of an unrelated disease.[62] In a substantial number of patients, the etiology will remain unclear until all relevant laboratory parameters have been collected or the patient exhibits additional signs and symptoms during longitudinal follow-up.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

We here propose a global classification for MCA-related conditions and disorders, including conditions predisposing to MCA. Predisposing conditions and pathologies include, among others, HαT, mastocytosis, atopic states, and overt allergies. Overt MCADs can be divided into MCASs, other MCADs, and unspecified MCA-like conditions, also referred to as unspecified MCA/MCAD or MCAD NOS. A diagnosis of MCAS requires fulfillment of all diagnostic consensus MCAS criteria; in other MCA-related or MCA-like conditions, MCAS criteria are not fulfilled. Still, such patients require attention, special treatment, and personalized medicine approaches. In many of the patients with suspected MCA or MCAS, other disorders may be diagnosed. Therefore, it is of great importance to consider differential diagnoses in these cases.

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