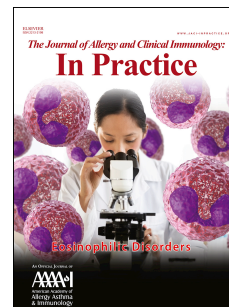


# Journal Pre-proof

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

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# Global Classification of Mast Cell Activation Disorders

## An ICD-10-CM-Adjusted Proposal of the ECNM-AIM Consortium

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Running Title: Global Classification of MCAD

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### **Authors' Contributions**

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**Abstract**

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 some patients, it may be difficult to prove MCA with certainty, 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 implicating suspected MCA behind such conditions are lacking, even if some of these conditions have recently been assigned to an 'international classification of disease-10-clinical modification' (ICD-10-CM) code. In this article, we discuss diagnostic features and criteria and propose a global ICD-10-CM-adjusted classification for disorders associated with MCA, herein referred to as MCA disorders (MCAD), with special emphasis on the delineation between confirmed MCAS, MCAD not fulfilling MCAS criteria, and suspected MCA disorder 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.

**Key words:** mastocytosis, mast cell activation, H $\alpha$ T, diagnostic criteria, MCAS

## List of Abbreviations

|                  |                                                                       |
|------------------|-----------------------------------------------------------------------|
| BM               | Bone marrow                                                           |
| CM               | Cutaneous mastocytosis                                                |
| EU               | European Community                                                    |
| H $\alpha$ T     | Hereditary alpha tryptasemia                                          |
| ICD-10-CM        | International classification of disease-10-clinical modification code |
| IgE              | Immunoglobulin E                                                      |
| IgG              | Immunoglobulin G                                                      |
| ISM              | Indolent systemic mastocytosis                                        |
| MC               | Mast cells                                                            |
| LT               | Leukotriene                                                           |
| MCA              | Mast cell activation                                                  |
| MCAD             | Mast cell activation disorder(s)                                      |
| MCAS             | Mast cell activation syndrome(s)                                      |
| MMAS             | Monoclonal mast cell activation syndrome                              |
| PGD <sub>2</sub> | Prostaglandin D <sub>2</sub>                                          |
| SM               | Systemic mastocytosis                                                 |
| US               | United States                                                         |
| WHO              | World Health Organization                                             |

## Introduction

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

The capacity of MC 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.<sup>11-15</sup> The severity of an anaphylactic reaction is further determined by the numbers of MC involved, cytokine exposure, the nature and number of triggers and co-factors (e.g., IgE-reactive allergens, non-steroidals, toxins such as within venoms), the type and amount of IgE, the presence of comorbidities (e.g., allergy, infectious diseases, mastocytosis), epigenetic factors, and

other patient-related variables (cardiovascular status, physical exercise, nutrition, alcohol, drugs).<sup>3,11-20</sup>

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.<sup>2,3,11-14,19</sup> Severe or even life-threatening MCA may develop when i) the burden of MC is high, and/or ii) when most or all MC are in a 'hyper-activated' state and release all their mediators massively and instantly, and/or iii) when comorbidities such as cardiovascular or pulmonary diseases contribute substantially to an MCA event. When hypersensitivity reactions are severe, systemic and recurrent, a MCA syndrome (MCAS) may be diagnosed.<sup>21-26</sup> Although in most of these patients, anaphylaxis is diagnosed, there are also patients who suffer from MCAS and fulfil 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 (EU/US-based) consensus group.<sup>21,22,24</sup> In addition, a diagnostic algorithm for MCAS has been developed.<sup>26</sup> 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.<sup>27-29</sup> 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 (MCAD) or non-specified MCA reactions or suspected MCA.<sup>27-29</sup> In these patients, local MCA, less severe MCA or MCA

potentially involving only a limited set of mediators or only one organ system, may be implicated, while other patients do not have a MCAD.

More recently, 'international classification of disease-10-clinical modification codes' (ICD-10-CM codes) have been created in the U.S. 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. In order 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 i) confirmed MCAS (and MCAS variants) and ii) other MCAD not fulfilling (all) diagnostic criteria to establish an MCAS, in contrast to cases of suspected MCAS which are ruled out by history or laboratory evaluation<sup>28</sup>.

## **Diagnostic Criteria and Classification of MCAS**

The diagnosis of MCAS is suspected when i) clinical symptoms are severe, ii) systemic, involving at least 2 organ systems, and iii) recurrent, most commonly in form of repeated anaphylaxis, and iv) evidence of involvement of MC is demonstrable.<sup>21,22,24-29</sup> Based on consensus criteria (Table 1), the diagnosis MCAS can be established when a) typical clinical symptoms arising from recurrent acute systemic (multi-organ) 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;

280 example: increase in serum tryptase from a basal level of 50 to 70:  $50+10$  [20%] = 60 +  
 281 2 = 62: any value beyond 62 counts as biochemical MCAS criterion) and c) the  
 282 symptoms respond to drugs blocking MCA, MC mediators, mediator production, or  
 283 mediator effects.<sup>21,24-28</sup> All 3 criteria must be fulfilled to conclude that the patient is  
 284 suffering from MCAS (Table 1). When the tryptase test is not available or inconclusive,  
 285 other biomarkers indicative of MC activation, such as an increase in histamine- or PGD<sub>2</sub>  
 286 metabolites in urinary samples (spot urine taken within a few hours after an event or  
 287 over a 24 hour period after an event) to more than 200% (+100%) of the individual's  
 288 baseline (measured in a symptom-free interval) in association with an event, may be  
 289 employed as alternative diagnostic marker, although this minimal diagnostic threshold  
 290 has not yet been validated (Table 1).<sup>26</sup>  
 291 When the diagnosis of MCAS has been established, the next essential step is to  
 292 determine the etiology and to classify MCAS.<sup>21,24-26</sup> Based on the underlying  
 293 condition(s), MCAS can be split into a) monoclonal (= clonal or primary) MCAS where  
 294 *KIT*-mutated, monoclonal (often CD25+) MC are detected and an underlying  
 295 mastocytosis is often found, b) secondary MCAS where an underlying non-neoplastic  
 296 disease, usually an IgE-dependent allergy, is detected, and c) idiopathic MCAS where  
 297 no underlying disease and no MC clonality that could explain MCA is found (Table  
 298 2).<sup>21,24-26</sup> Monoclonal MCAS, also abbreviated as MMAS, may also develop in patients  
 299 with *KIT*-mutated (usually *KIT* D816V+) MC in whom the diagnostic criteria for  
 300 mastocytosis are not all fulfilled.<sup>21,24-26,30,31</sup> In some of these patients, overt systemic  
 301 mastocytosis (SM) may develop during follow up.  
 302 In a substantial number of cases, monoclonal (primary) as well as secondary MCAS  
 303 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 2).<sup>32-37</sup> 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.<sup>32-37</sup> These patients are candidates for life-long immunotherapy and in selected cases can also be considered to be candidates for IgE-targeting antibody therapy (e.g., omalizumab) with the aim of preventing severe MCAS events.<sup>37-45</sup> 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 (H $\alpha$ T) and documented MCAS should be classified as primary MCAS, secondary MCAS, or as idiopathic MCAS when no other underlying etiology or disease is detected. Since H $\alpha$ T is not a clonal disease but rather a genetic trait, and the exact relationship between H $\alpha$ T and anaphylaxis remains unclear, this question remains open. One approach would be to call this condition H $\alpha$ T-associated (H $\alpha$ T+) MCAS (Table 2).

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 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 MCAS patients when all MCAS criteria are fulfilled.

## **Predisposing Conditions and Pathologies that may contribute to the Etiology and Manifestation of MCAS and other MCAD**

A number of underlying pathologies, predisposing genetic conditions, and co-morbidities have been identified as potential triggers of MCA and thus co-factors relevant to the manifestation of MCAS and other MCAD (Table 3). 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.<sup>32-37,44</sup> There are also IgE-independent (e.g., IgG- 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.<sup>3,46</sup> Local inflammatory reactions and (viral or bacterial) infections may also induce or aggravate anaphylactic reactions so that an MCAS or other MCAD is diagnosed.

In systemic mastocytosis (SM), the lifetime risk of anaphylaxis has been reported to be 30-40%. Patients with SM have a high risk to develop severe mediator-related symptoms and MCAS for several reasons.<sup>33-37,44</sup> First, the numbers of the initial cells involved (MC) can greatly increase in patients with SM. Second, MC in SM are presumed to be in an activated state, especially when these patients are also carriers of H $\alpha$ T and/or suffer from an allergic disease.<sup>33-37,44</sup> Finally, the *KIT* D816V mutation has been implicated in MCA, because KIT activation by its ligand, stem cell factor, can also trigger MCA and sensitize MC against IgE-dependent stimuli.<sup>16,17</sup> Indeed, activating mutations in the *KIT* gene are commonly detected in patients with SM.<sup>47</sup> However, expression of *KIT* D816V in MC lines does not necessarily lead to increased releasability.<sup>48</sup> Rather in some

experimental models, *KIT* D816V even seems to down regulate MCA.<sup>48</sup> Correspondingly, many patients with SM do not suffer from any MCA-related events, even if the burden of MC 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 MC.<sup>34-37</sup> 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) such as the MC maturation stage and/or expression levels of IgE receptors on MC.<sup>3,14,19,49</sup> Finally, any type of mastocytosis, including variants of cutaneous mastocytosis (CM) and variants of systemic mastocytosis (SM) can predispose to the development of an MCAS, localized MCA (often in the skin) or another MCAD (Table 3 and Table 4).

More recently, hereditary alpha tryptasemia (H $\alpha$ T) 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.<sup>15,50-55</sup> Moreover, the H $\alpha$ T carrier status is more prevalent in patients with SM (15-20%) compared to the general (otherwise healthy) population (around 5%).<sup>15,54</sup> In most individuals with H $\alpha$ T the serum tryptase level is slightly to markedly elevated, but may in some H $\alpha$ T carriers be within normal range.<sup>15,50-56</sup> In those H $\alpha$ T carriers who are also suffering from SM, the serum tryptase levels are usually higher than one would expect from the burden of neoplastic MC detected by histology in the bone marrow.<sup>54</sup> Whether H $\alpha$ T per se can cause MCA or even MCAS (in the absence of an allergy and/or mastocytosis) remains uncertain. H $\alpha$ T carriers do not have increased levels of other MC mediators, and MC carrying H $\alpha$ T genotype do not appear to be more

sensitive to specific IgE-mediated degranulation *in vitro*.<sup>50</sup> Moreover, most H $\alpha$ T carriers are asymptomatic or suffer only from mild mediator-induced symptoms, so that based on existing information, we are of the opinion that H $\alpha$ T 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.<sup>15,50-56</sup>

Table 3 shows a summary of underlying pathologies, co-morbidities and conditions predisposing to MCAS and other MCAD, and Table 4 shows a compilation of pathologies and conditions together with the related ICD-10-CM codes.

#### **Other MCAD: 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 MC 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 (e.g., 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

397 meet the 120%+2 ng/ml threshold. In these patients, the term 'MCA disorder (MCAD)'  
 398 or 'other MCAD' may be appropriate (ICD-10-CM code: D89.49) (Table 4).<sup>29</sup> These  
 399 patients should be managed and treated in the same way as those with MCAS. In fact,  
 400 these patients usually respond to drugs targeting MCA, MC mediators or mediator  
 401 effects in the same way as patients with MCAS. It is also appropriate to ask for other  
 402 MC mediators in these patients. Some of these patients can be re-classified as MCAS  
 403 when tryptase and/or other MC-related mediators increase substantially during an attack  
 404 in a subsequent investigation.<sup>57-60</sup> In some of the patients, the levels of urinary PGD<sub>2</sub>  
 405 metabolites may increase substantially but serum tryptase levels increase only slightly.  
 406 These patients may be classified as MCAS or other MCAD, depending on the  
 407 symptomatology and the degree to which the MC mediators increase over the  
 408 individual's baseline. For example, a patient with a massive increase in urinary  
 409 histamine- and/or PGD<sub>2</sub> metabolite (more than +100% = >200% of the individual's  
 410 baseline and above normal range for the assay) and some event-related increase in serum  
 411 tryptase, could be classified as MCAS. The minimal diagnostic threshold-increase in  
 412 urinary histamine- or PGD<sub>2</sub> metabolites for a (other) MCAD should be 50% over the  
 413 individual's baseline (>150% total). The proposed thresholds for these urinary  
 414 biomarkers of MC activation are based on limited available data, and clinical validation  
 415 studies are thus needed to support their clinical value in daily practice. Clinical features  
 416 and criteria proposed for the group of patients suffering from 'other MCAD' not  
 417 fulfilling MCAS criteria (ICD-10-CM code: D89.49) are depicted in Table 5.  
 418 In other patients, the clinical symptoms of MCA are less clear and there is only  
 419 indication of a local or systemic reaction that presents some features of MCA but would  
 420 not qualify as MCAS criteria.<sup>26-29</sup> For example, such patients may exhibit urticaria, with

421 findings thus compatible with local MCA. In other patients, symptoms may be mild and  
 422 involve only one organ, or are not typical for MCA and MCAS. Examples are isolated  
 423 gastrointestinal symptoms (cramping, diarrhea, constipation, food intolerance), isolated  
 424 skin symptoms (flushing, pruritus, edema, nondescript rash), or isolated neurological or  
 425 psychiatric symptoms (headache, fatigue, brain fog, depression, seizures, focal  
 426 neurologic deficits, psychosis). In most such instances, serum tryptase levels and other  
 427 MC-derived mediators do not increase substantially (diagnostic increase over the  
 428 individual's baseline not reached) during a symptomatic event. Some of these patients  
 429 may also have typical signs and symptoms indicative of a localized MCA and related  
 430 co-morbidities, such as an IgE-mediated rhino-conjunctivitis or atopic dermatitis, which  
 431 are common in the diagnosis 'MCA, unspecified' or general population. In these  
 432 patients, the term 'MCAD unspecified' is not justified. For atopic symptoms, we  
 433 recommend using ICD-10-CM codes specific for the atopic entity and not using the term  
 434 'MCAD unspecified' as an overarching diagnosis. In particular, the certainty that MC  
 435 are indeed responsible for the reported symptoms in such a patient remains questionable  
 436 (unconfirmed). Thus, an 'unspecified MCA/MCAD' should not be considered a final  
 437 diagnosis but should prompt the physician to search for additional (more definitive)  
 438 indications (criteria) of MCA and for diseases in the differential diagnosis.<sup>26-29</sup> Indeed,  
 439 an 'unspecified MCA/MCAD' may turn out not to be MCA/MCAD in more detailed  
 440 investigations. The designated ICD-10-CM code for cases of unspecified (unconfirmed)  
 441 MCA/MCAD is D89.40 (Table 4). Diagnostic clinical features (potential diagnostic  
 442 criteria) proposed for these patients are shown in Table 5. It should be noted that it is  
 443 usually impossible to establish a definitive relationship between the symptomatology  
 444 and involvement of MC 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 4). 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 in order to avoid misunderstanding and misdiagnoses. However, we also note that although this proposal is an important first step towards 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 MC and other cell types.

#### **Proposed Global Classification of MCAD and Predisposing Conditions**

A proposed global classification of MCAD and of predisposing conditions is presented in Table 4. In this classification, MCAD, which represents the unifying umbrella term of all MCA-related conditions, is essentially divided into MCAS, other MCAD and unspecified MCA (MCAD, unspecified or not further specified=NOS). MCAS in turn are split into several variants depending on the underlying (known) etiology (Table 2). Whereas in all MCAS variants, all 3 MCAS consensus criteria must be fulfilled, this is not the case in other MCAD and in cases with unspecified MCAD (Table 2, Table 5).<sup>21-</sup>  
<sup>29</sup> In 'other MCAD', definitive signs and symptoms of MCA and thus evidence of MC involvement have been documented (Table 5). By contrast in patients with unspecified MCAD /MCAD, NOS), MC involvement may be suspected, but a MC disorder is not

present (Table 5). The proposed global classification of MCAD is in line with a proposed refined classification of all MC disorders recently published by our consensus group.<sup>29</sup>

### **Proposed Diagnostic Algorithm for Patients with Suspected MCAD**

Figure 1 provides a diagnostic algorithm for patients with suspected MCAD and a related classification of MCAD. 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 a 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 three MCAS criteria are fulfilled (Table 1), 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 (co-morbidities), and potential triggers of MCA (Table 2). Based on this information, the MCAS variant defined by the consensus classification (and ICD-10-CM code) will be established (Figure 1). As shown in Table 5, the diagnosis ‘other MCAD’ (ICD-10 CM code: D89.49) entails a suspected MC disorder in which criteria to diagnose MCAS (as shown in Table 1) are not completely fulfilled. In such patients, presence of a MC disorder is not corroborated with certainty; this diagnosis should not be used routinely in patients with multi-system symptoms and a lack of confirmatory criteria.<sup>28</sup> The diagnosis ‘MCA/MCAD, unspecified’, MCAD, NOS (ICD-10-CM code:

D89.40) entails a suspected MC disorder, but with no MC involvement based on clinical signs or symptoms or documented via laboratory evaluation. Such patients do not exhibit a salutary response to drugs targeting MC or MC mediators. In these patients, MCAS criteria are not fulfilled, and presence of a MC disorder is not confirmed.<sup>28</sup> 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 (DD) to consider when examining a patient with suspected MCAS and other MCAD.<sup>3,21-28</sup> These are often disorders that can mimic various symptoms of anaphylaxis with severe hypotension.<sup>3,21-28</sup> These differential diagnoses include, among others, cardiovascular disorders, dehydration, septicemia, acute bleeding, intoxications, dysautonomia, anxiety and somatoform disorders and psychiatric conditions. By contrast, differential diagnoses to 'other MCAD' or 'unspecified MCA/MCAD' are many more as 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.<sup>26,28</sup> Alternative diagnostic criteria for MCAS have also been proposed<sup>61</sup>, 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, resulting in potential harm<sup>62</sup>. 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, H $\alpha$ T, mastocytosis, atopic states, and overt allergies. Overt MCA disorders can be divided into MCAS, other MCA disorders, and unspecified MCA-like conditions, also referred to as unspecified 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.

534

535 **Authors' Contributions**

536 All authors contributed equally by discussing data, literature material, and case reports  
537 during the project period (March 2020 until October 2021). All authors contributed  
538 substantially to the study by establishing the concept and algorithm and by writing parts  
539 of the manuscript. All authors approved the final version of the document.

540

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## Legend to Figures

### Figure 1

Proposed diagnostic algorithm for patients with suspected mast cell activation disorders (MCAD) and mast cell activation syndromes (MCAS).

Not uncommonly, patients may suspect or have been labeled as having MCAS but have symptoms without clear relation to MC activation (MCA) and do not fulfill MCAS criteria; other etiologies (DD) are important to explore in these patients. In patients with typical clinical features and symptoms of a mast cell (MC) activation, the physician will establish the provisional diagnosis of a MC activation disorder (MCAD). In addition, the physician will consider signs and symptoms of anaphylaxis, criteria of MCAS, and potential differential diagnoses (DD). MCAS is diagnosed when all three MCAS criteria are fulfilled: (1) typical (MCA-related) clinical symptoms; (2) an event-related increase in serum tryptase; 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 (co-morbidities), and potential triggers of MC activation, 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 5), 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 multi-system symptoms. In these patients, the condition should be described in sufficient detail, and triggering factors and underlying etiologies 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 multi-system symptoms. In these cases, it is usually difficult or impossible to define the impact of MC, 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 DD in these cases. Finally, in all groups of patients, a management plan should be established.

## Tables

Table 1

Diagnostic consensus criteria for mast cell activation syndrome (MCAS)\*

A) Typical clinical signs of severe, recurrent (episodic) systemic mast cell activation are present (often in the form of anaphylaxis) (definition of systemic: involving at least two organ systems)

B) Involvement of MC 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 hour or spot urinary histamine- metabolites or PGD<sub>2</sub>-metabolites) may also be employed, but are less specific compared to the increase in serum tryptase. 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 is inconclusive. A proposed diagnostic threshold is >200% of the individual's baseline (increase by more than +100%) provided that the test result is above the normal range for the assay.

\*\*\*Example: histamine receptor blockers.

Abbreviations: MC, mast cells; PGD<sub>2</sub>, prostaglandin D<sub>2</sub>.

Table 2

Recognized variants of mast cell activation syndromes (MCAS) 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<br>= clonal MCAS*<br>= primary MCAS* | the <i>KIT</i> D816V mutation is detected and mast cells may display CD25 and/or CD30<br>a) confirmed mastocytosis (CM or SM)**<br>b) only two 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 MC or <i>KIT</i> D816V is found*** | ++                                             |
| Combined MCAS                                        | Criteria for primary MCAS and secondary MCAS are fulfilled, and H $\alpha$ T may also be detected****                                                                                           | +++                                            |
| H $\alpha$ T+ MCAS                                   | Hereditary alpha tryptasemia (H $\alpha$ T) 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, no neoplastic/clonal MC is detected*****, and no H $\alpha$ T is known or found                   | +                                              |

\*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 two 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 MC activation and thus MCAS.

\*\*\*\*Patients with a combined H $\alpha$ T+ 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 MC.

Abbreviations: MC, mast cells; MCA, mast cell activation; CM, cutaneous mastocytosis; SM, systemic mastocytosis.

Risk score: +, low risk; ++, high risk; +++, exceptionally high risk

Table 3

Conditions and co-morbidities predisposing to the development of anaphylaxis and MCAS or other MCAD, and potentially underlying or known mechanisms

| Condition/disease                                 | Potential underlying mechanism(s)                                                                                                                                              |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>Genetic/hereditary:</u>                        |                                                                                                                                                                                |
| Hereditary alpha tryptasemia (H $\alpha$ T)       | Increased sensitivity to certain triggers (example: $\alpha/\beta$ -tryptase-induced cleavage of mechanosensory receptors, leading to vibration-triggered degranulation of MC) |
| Atopic diathesis                                  | Increased numbers of tissue MC<br>Increased tissue inflammation triggered by auto-allergens and related exogenous allergens through multiple mechanisms                        |
| <u>Predisposing co-morbidities:</u>               |                                                                                                                                                                                |
| <u>Hypersensitivity disorders:</u>                |                                                                                                                                                                                |
| IgE-dependent allergies                           | IgE-dependent activation of MC                                                                                                                                                 |
| IgE-independent hypersensitivity                  | MC activation by other triggers, such as IgG, or complement components.                                                                                                        |
| Atopic disorders with chronic tissue inflammation | IgE-dependent activation of MC and cytokine/chemokine-induced activation of MC 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                                                                     |
| <u>Other disorders potentially involving MC:</u>  |                                                                                                                                                                                |
| Autoimmune disorders involving MC                 | Chronic activation of MC in inflamed tissues (IgE-, IgG-, or complement-mediated)*                                                                                             |
| Chronic inflammatory diseases involving MC        | Chronic activation of MC in inflamed tissues (complement- or cytokine-mediated)*                                                                                               |
| Infectious diseases involving MC                  | 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. MC, mast cells; MCAS, mast cell activation syndrome; MCAD, mast cell activation disorders; IgE, immunoglobulin E, IgG, immunoglobulin G.

Table 4

Mast Cell Activation(-Related) Disorders (MCAD), Predisposing Conditions, and official ICD-10-CM Codes

| Disorder/condition                                            | Abbreviations | ICD-10-CM code |
|---------------------------------------------------------------|---------------|----------------|
| <u>Mast cell activation-related disorders (MCAD):</u>         |               |                |
| 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*        |
| <u>Conditions predisposing to MCA/MCAD:</u>                   |               |                |
| 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        | + 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 shown in Supplementary Table S11. However, it should be mentioned that these criteria should not be use 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.

Abbreviations: IgE, immunoglobulin E; HαT, hereditary alpha tryptasemia; ICD-10-CM codes; CM, cutaneous mastocytosis; BMM, bone marrow mastocytosis; ISM, indolent systemic mastocytosis; SSM, smoldering SM; ASM, aggressive SM; SM-AHN, SM with an associated hematologic neoplasm; MCL, mast cell leukemia; MCS, mast cell sarcoma; ICD-10-CM code, International statistical classification of disease-10-clinical modification code; MCA, mast cell activation.

Table 5

Diagnostic Features of Mast Cell Activation-Related Disorders (MCAD) that do not fulfil 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 mast cell activation in one or more organs, mast cell involvement not reconfirmed with certainty, symptoms may be chronic, less severe and recurrent, and often involve only one organ system*<br>b) Patients may or may not respond to drugs targeting mast cells or mast cell mediators<br>c) MCAS criteria are not fulfilled<br>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 one or more organ systems (with or without signs of anaphylaxis)<br>b) Event-related increase in a mast cell-specific mediator (substantial increase in serum tryptase but below the MCAS threshold) or substantial increase in urinary histamine- or PGD <sub>2</sub> -metabolite***<br>c) Response of symptoms to drugs targeting mast cell activation, mast cell mediators, or mediator-effects (mediator-receptors)<br>d) Criteria to diagnose MCAS are not completely fulfilled (sometimes one or two out of the three mandatory MCAS criteria are met)**<br>e) Often inappropriate to explain multisystem symptoms and should not be used as a primary or final diagnosis |

\*No robust validated diagnostic criteria are available for these conditions to date. Unspecified or 'not otherwise specified (NOS)' means that involvement of the mast cell 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 mast cells.

Abbreviations: MCAD, mast cell activation(-related) disorder; MCAS, mast cell activation syndrome; ICD-10-CM, International statistical classification of diseases-10-clinical modification code; NOS, not otherwise specified; PGD<sub>2</sub>, prostaglandin D<sub>2</sub>.

\*\*In these patients (2 out 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'

1036 and would change to definitive MCAS at the time when a response to therapy has been  
1037 documented.  
1038 \*\*\*An increase in histamine- or PGD<sub>2</sub>-metabolite by at least 50% over the individual's baseline  
1039 (total >150% of baseline and value must be above the normal range for the assay) should qualify  
1040 as an indication (criterion) of an MCAD (other MCAD).

