

Mast Cell Activation Syndromes: Collegium Internationale Allergologicum Update 2022



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Keywords

Mast cells · IgE · Tryptase · Mast cell activation syndrome (MCAS) · Diagnostic MCAS criteria · Classification

Abstract

Mast cell activation syndromes (MCASs) are defined by systemic severe and recurrent mast cell activation, usually in form of anaphylaxis, a substantial, event-related increase of the serum tryptase level beyond the individual's baseline and a response of the symptomatology to drugs directed against mast cells, mast cell-derived mediators, or mediator effects. A number of predisposing genetic conditions, underlying allergic and other hypersensitivity states, and related comorbidities can contribute to the clinical manifestation of MCASs. These conditions include hereditary alpha tryptasemia, mastocytosis with an expansion of clonal *KIT*-mutated mast cells, atopic diathesis, and overt IgE-dependent and IgE-independent allergies. Several of these conditions have

overlapping definitions and diagnostic criteria and may also develop concomitantly in the same patient. However, although criteria and clinical features overlap, each of these conditions is characterized by a unique constellation of variables and diagnostic criteria. Since two, three, or more conditions can coexist in the same patient, with obvious clinical implications, it is of crucial importance to diagnose the variant of MCAS precisely and to take all accompanying, underlying and potentially complicating conditions, and comorbidities into account when establishing the management plan. Indeed, most of these patients require multidisciplinary investigations and only a personalized treatment approach can lead to an optimal management plan providing an optimal quality of life and low risk of anaphylaxis.

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Introduction

Mast cells (MC) are critical effector cells of local and systemic hypersensitivity reactions and other immediate or chronic inflammatory conditions [1–3]. MC display high-affinity immunoglobulin E (IgE)-binding sites and store an array of vasoactive and inflammatory mediators in their granules [1–5]. During an IgE-dependent anaphylactic reaction, allergen-mediated cross-linking of IgE receptors (IgER = FcεRI) results in an “explosive” release of these mediators [1–6]. Blood basophils also contribute to allergic reactions as these cells also exhibit cell surface IgER and contain numerous mediator substances, including histamine and arachidonic acid metabolites [1, 7]. MC and basophils may also be activated by other stimuli, including cytokines, chemokines, complement components, IgG, microbes, drugs, and toxins through specific receptors expressed by these cells [1–3, 7–9].

The capacity of MC and basophils to release mediators of allergy upon activation, often referred to as releasability, depends on a number of variables, including the genetic background, the nature and source of the allergen, additional cofactors (e.g., exercise, stress, alcohol, drugs), underlying diseases (e.g., infections) and contributing comorbidities, numbers of MC or basophils participating in the reaction, the type and amount of IgE, the cytokines and chemokines involved, and the signaling cascades that are activated upon ligand-induced activation [3–6, 10–14]. MC activation (MCA) can be observed in a number of different pathologic conditions in children and adults. Acute MCA is quite often seen in patients suffering from allergic disorders with the most severe manifestation being anaphylaxis [1–6]. Severe or even life-threatening MCA may occur when the burden of MC is high and/or the involved MC are in a “hyperactivated” state, resulting in increased releasability [2–5, 8, 9]. In such events, the serum tryptase level increases substantially over the individual’s baseline and returns to the individual’s “pre-event range” after several hours in the symptom-free interval [15–17].

When the resulting clinical symptoms are severe, systemic, and recurrent (recurrent anaphylaxis), an MCA syndrome (MCAS) may be diagnosed [18–22]. Depending on the etiology, MCAS can be divided into primary MCAS where clonal MC are detected, secondary MCAS where an IgE-related allergy, other allergic disorders (mediated by IgE-independent mechanism), or another reactive disease process triggering MCA is documented, and idiopathic MCAS where no underlying disease or etiology is identified [18–22]. Especially in patients with severe

allergies and in those who suffer from mastocytosis and a concomitant allergy, the risk to develop an MCAS event is rather high and in several of these patients, such severe events of anaphylaxis may be life-threatening [20–23].

More recently, additional genetic features have been linked to an elevated risk to develop anaphylaxis and MCAS. One such factor is hereditary alpha tryptasemia (HaT), a genetic trait defined by extra copies of the *TPSAB1* gene encoding for alpha tryptase, and an elevated basal serum tryptase concentration in most carriers [24–26]. In patients with systemic mastocytosis (SM), the HaT carrier status is associated with a high prevalence of severe mediator-related symptoms and with concomitant allergies [27, 28]. Patients with SM who are HaT carriers and are also suffering from an IgE-dependent allergy may bear the highest risk to develop anaphylaxis and MCAS [26–28].

During the past few years, a discussion about the etiology, diagnosis, and optimal management of patients with MCAS has been initiated [8, 21–23]. This discussion is useful and may lead to a better appreciation and understanding of underlying or contributing mechanisms and to the development of improved strategies to therapeutically interfere with MCA, MC expansion, and abnormal signaling pathways in these cells. In the current manuscript, we discuss cellular, molecular, and mechanistic relationships between SM, MCAS, allergy, HaT, and atopic diathesis. In addition, we compare diagnostic criteria and discuss overlapping features defining these conditions. Finally, we discuss implications that arise from the observation that two or even more of these conditions can co-exist in the same MCAS patient, which is a clear challenge in clinical practice and can only be addressed appropriately by developing individualized management strategies and personalized treatment approaches [22, 23].

Clinical Manifestations and Laboratory Correlates of MCA

MCA may occur in a number of different physiologic and pathologic conditions. Acute MCA is commonly seen in various allergic reactions, other hypersensitivity reactions (e.g., intolerance) and toxic reactions against exogenous elicitors, such as venoms [4, 8, 9, 19–23, 29]. The most common underlying condition is an overt IgE-dependent allergic disorder. In these patients, severe, recurrent systemic MCA may lead to the clinical picture of anaphylaxis [2–5, 8, 9]. As mentioned before, serum total tryptase concentrations increase substantially above the

Table 1. Symptoms of MCA*

Form of MCA	Typical symptom(s)	Mechanisms and mediators involved
Local MCA**	Flush, erythema Pruritus Urticaria, hives Local angioedema Rhinitis, sneezing Cough, dyspnea Diarrhea	Histamine Histamine Histamine Histamine, VEGF Histamine Histamine, PGD ₂ , cytokines Histamine
Mild systemic MCA**	Mild hypotension without shock Mild headache Cough, mild dyspnea Mild diarrhea, loose stool Nausea Mild abdominal cramping	Histamine, PGD ₂ , chemokines Histamine Histamine, PGD ₂ , cytokines Histamine Histamine Histamine, cysLT, chemokines
Severe systemic MCA	Severe acute hypotension (anaphylactic shock) Severe constitutional symptoms (sweats, fever, unconsciousness) Severe skin problems (wheals, itching, angioedema) Acute respiratory problems: hypoxia, wheezing, asthma (dyspnea, stridor, bronchospasm) Acute gastrointestinal symptoms (cramping, vomiting, diarrhea)	Histamine, cytokines Histamine, cytokines Histamine, PGD ₂ , cysLT Histamine, PGD ₂ , cytokines Histamine, cysLT, chemokines
Chronic systemic MCA**	Chronic tissue inflammation/atopic tissue inflammation ("itis") Chronic skin problems Chronic diarrhea and/or nausea Chronic cough Fatigue Depression and other neuropsychiatric symptoms	Cytokines, proteases Cytokines, cysLT, PGD ₂ Histamine, cytokines Histamine, cysLT Histamine, cytokines Histamine, cytokines

MCA, mast cell activation; MCAD, mast cell activation disorder; MCAS, mast cell activation syndrome; PG, prostaglandin; PAF, platelet-activating factor; cysLT, cysteinyl leukotrienes LTC₄, LTD₄, and LTE₄. * The table shows most typical and frequently documented symptoms and findings. However, many more signs and symptoms indicative of the presence of MCA have been reported. ** In patients with local or less severe forms of MCA, an MCAD may be diagnosed even if MCAS criteria are not met. According to the ICD-10 code, these conditions are called other or unspecified MCAD, whereas MCAS is an MCAD where all MCAS criteria are fulfilled.

individual's baseline during an anaphylactic event in most of these patients, peak at around 2 h after the event, and return to baseline 4–12 h after complete resolution of symptoms [15–17].

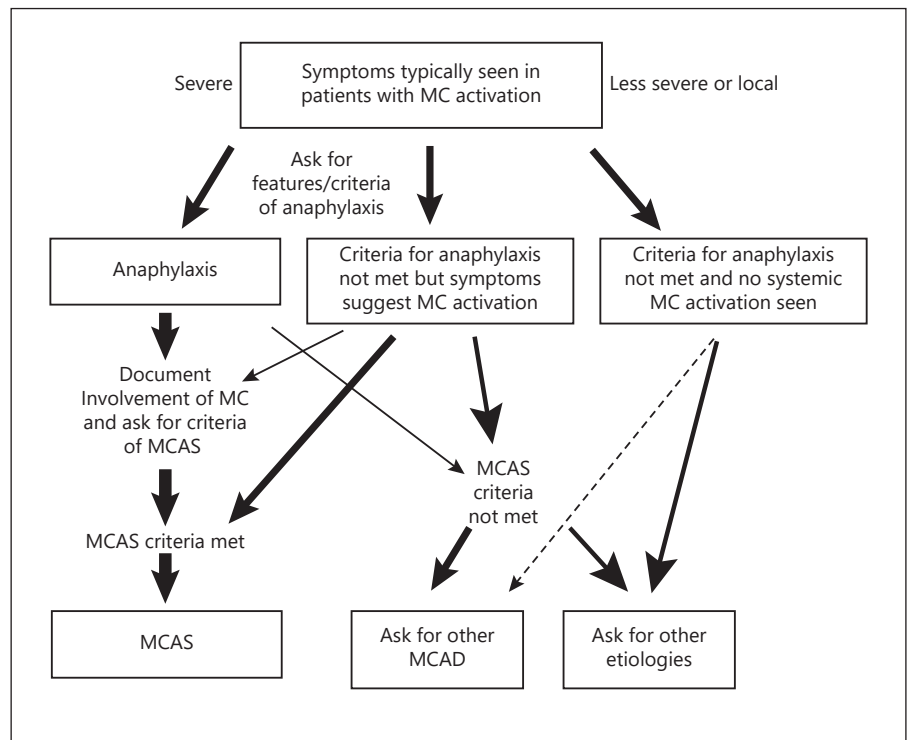
Other mediators produced and stored in MC, such as histamine and its metabolites or PGD₂ and its metabolites, are also released from these cells during anaphylaxis and therefore increase in biological fluids (plasma, urine) during and shortly after an anaphylactic episode [30–36]. Compared to serum tryptase levels, these MC-dependent compounds may sometimes be more sensitive parameters (biomarkers) in allergic reactions and thus also detected as elevated in less severe or chronic forms of MCA but are clearly less specific for the MC lineage and less well validated in MCAS contexts compared to tryptase.

The typical clinical symptoms that can be documented in patients with MCA are shown in Table 1. In those with

severe systemic symptoms, several different organs may be involved and the symptoms usually correspond to the various grades of anaphylaxis [37–41]. Additional typical symptoms of MCA include, among others, hypotension (syncope), urticaria, flushing, angioedema, wheezing, headache, nausea, cramping, vomiting, and diarrhea (Table 1) [8, 37–41].

Also very common are local forms of MCA, less severe (mild) MCA-dependent reactions, and conditions associated with chronic, but not acute, MCA. Related clinical symptoms are shown in Table 1. In these patients, MCA is usually more difficult to diagnose compared to acute severe systemic MCA. Examples are local allergic reactions to exogenous allergens and organ-related atopic disorders, such as allergic rhinoconjunctivitis, atopic dermatitis, urticaria, or allergic asthma [42–46].

Fig. 1. Approach to patients with suspected MCAS. In a first step, patients are examined for typical symptoms of MCA. In some of these patients, the symptoms are compatible with the diagnosis of anaphylaxis which increases the likelihood that the patient has an MCAS. In other patients, criteria for anaphylaxis are not met but symptoms still suggest MCA. In both groups, criteria for MCAS are applied. When MCAS criteria are met, the diagnosis MCAS is established, and the type of MCAS is defined. When MCAS criteria are not fulfilled, the patient may still suffer from MCA or a MCAD, for example, local MCA or a less severe form of MCA. When symptoms of MCA are mild, only local, or no signs for MCA are found, it is important to ask for alternative etiologies. In these patients, no symptoms of anaphylaxis are found, and serum tryptase levels do not increase over baseline during symptoms. Thicker arrows indicate the main-lines in the algorithm. In a very few patients without evidence of MCAS, the physician may ask for signs and symptoms of other MCAD (dashed line).



In most of these patients, serum tryptase levels increase only slightly or do not increase over the individual's baseline. Even the other MC-dependent compounds mentioned above, although more sensitive, may not increase in biological fluids in these patients. Therefore, these cases often represent a clinical challenge as diagnostic criteria for MCA or an MCAS are not fulfilled and the involvement (and primary role) of other inflammatory effector cells apart from MC, such as basophils or eosinophils, cannot be excluded. The final diagnosis in these cases remains descriptive and MC involvement can only be discussed [22, 47]. In most reports, these conditions are termed unspecified (unconfirmed) MCA disorders (unspecified).

In other patients, systemic severe MCA is detected, but the criteria for MCAS are not yet or not completely fulfilled. For example, patients may fulfill all clinical criteria and the serum tryptase level increase, but the increase over baseline does not fulfill the $120\% + 2 \text{ ng/mL}$ threshold. These patients are often termed "other MCA disorders" but cannot be called MCAS. In many cases, an IgE-dependent allergy is diagnosed. In another group of patients, tryptase levels are constantly elevated and may point to an occult form of mastocytosis, another myeloid neoplasm, or HaT. In most cases, a HaT will be diag-

nosed. However, the diagnosis of HaT per se or an IgE-dependent allergy per se is not diagnostic for MCAS even if MCAS-like symptoms have been recorded [22, 47]. Rather, MCAS can only be diagnosed in allergic patients when MCAS criteria are fulfilled and the same holds true for mastocytosis [18–20, 22, 47].

Diagnostic Criteria and Classification of MCAS

The diagnosis of MCAS has to be considered when symptoms of MCA are severe, systemic (involve more than 1 organ systems), and recurrent, usually in form of severe anaphylaxis, and the involvement of the MC lineage can be confirmed with certainty [18–23]. In principle, the diagnostic approach to these patients is simple and follows a step-wise approach (Fig. 1). In a first step, the physician asks for symptoms of MCA and anaphylaxis. Then, MCAS criteria are applied (Fig. 1). Based on diagnostic criteria proposed by the EU/US consensus group [19], the diagnosis MCAS can then be established when (a) typical clinical symptoms arising from recurrent acute systemic MCA (resembling recurrent anaphylaxis) have been documented, (b) MC-derived mediators increase substantially in the serum (tryptase) or urine (his-

Table 2. Classification of MCAS

Variant of MCAS	Main diagnostic features
Primary MCAS (clonal MCAS)*	The <i>KIT</i> D816V mutation is detected, and MCs aberrantly display CD25 in most cases (a) with confirmed mastocytosis (CM or SM)** (b) with only two minor SM criteria**
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***
HaT+ MCAS (familial/hereditary MCAS)	Criteria to diagnose MCAS are met, no related allergy or underlying clonal MC disease is detected, and the HaT test is positive****
Mixed forms of MCAS	MCAS criteria are fulfilled, and patients are suffering from two or more of the following: (a) CM or SM; (b) overt allergy/atopic disease; (c) a known genetic predisposition like HaT
Idiopathic MCAS	Criteria to diagnose MCAS are met, but no related reactive disease, no IgE-dependent allergy, no HaT, and no neoplastic/clonal MC are found***

MC, mast cells; MCA, MC activation; CM, cutaneous mastocytosis; SM, systemic mastocytosis; MMAS, monoclonal mast cell activation syndrome. * The terms clonal MCAS and MMAS can be used synonymously with the term primary MCAS. ** Most of the patients suffer from CM or SM. However, in some cases, only two minor SM criteria are detected, and criteria for SM and CM are not fulfilled. *** No *KIT* mutation at codon 816 is detected, and flow cytometry (if performed) will not detect a clonal population of CD25-positive MC. **** In HaT carriers without an allergy and/or SM, the incidence of anaphylaxis and thus MCAS is very low. Therefore, most of these patients have a mixed form of MCAS: in fact, these patients suffer from a concomitant allergy and/or SM. Whether a pure form of hereditary (HaT+) MCAS indeed exists is currently under debate.

Table 3. Delineation of conditions relevant to the classification of MCAS

Condition	Basic definition	Typical findings
<i>I. Predisposing conditions</i>		
Atopic diathesis (atopy)	Hereditary or constitutional predisposition to develop an allergic disease	Elevated IgE, atopic/allergic disease in case or family history
HaT	Increased copy number of the <i>TPSAB1</i> gene encoding for alpha tryptase	Elevated basal serum tryptase (in >90%) and familial clustering
<i>II. Overt clinical disorders/conditions/syndromes</i>		
Allergic diseases	Hypersensitivity against exogenous antigens/allergens	Overt allergic disease (trigger-dependent)
Atopic diseases	Hypersensitivity against exogenous and endogenous antigens/allergens	Overt atopic disease (often chronic and not dependent on exogenous triggers)
Mastocytosis	Expansion and accumulation of clonal MCs – WHO criteria for CM or SM met	Typical pathology and clinical findings in SM <i>KIT</i> D816V is usually detected in BM cells
IgE, immunoglobulin E; WHO, World Health Organization; CM, cutaneous mastocytosis; SM, systemic mastocytosis; BM, bone marrow.		

tamine or prostaglandin-D2 metabolites) over the individual's baseline (standard test: documented increase in serum tryptase levels following the 120% + 2 ng/mL formula), and c) the symptoms respond to drugs blocking MCA, MC mediators, mediator production, or mediator effects (Table 2) [18–20]. All of these 3 criteria must be

fulfilled to conclude that the patient is suffering from MCAS (Table 2). The clinical impact and robustness of these MCAS criteria have been confirmed in several validation studies and are regarded as widely accepted standard [48–50].

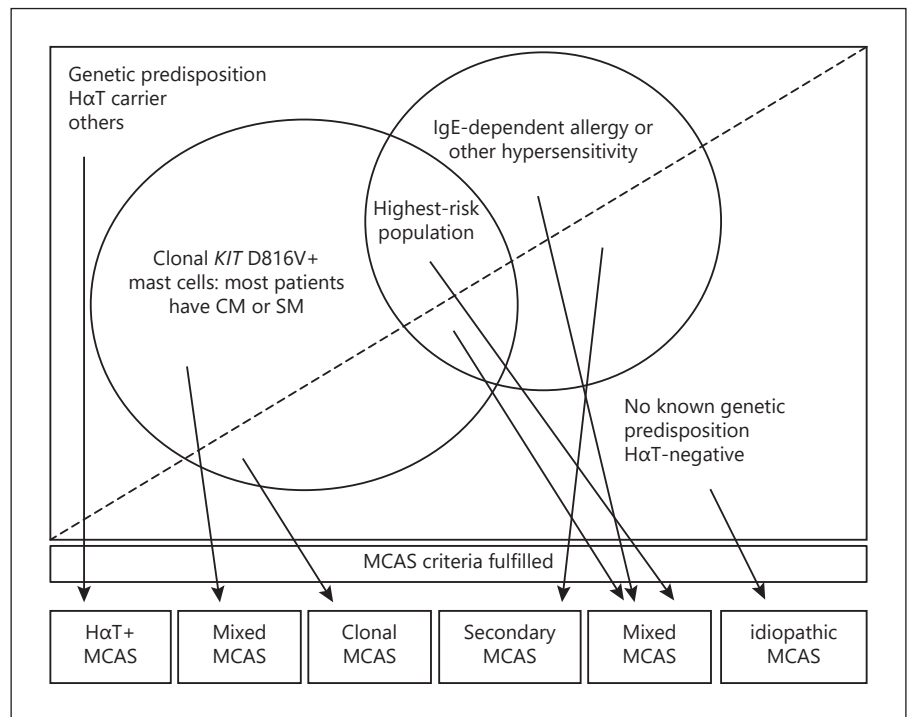


Fig. 2. Figure classification of MCAS based on underlying etiologies and disorders. When MCAS criteria are fulfilled, patients are examined for the presence of clonal *KIT*-mutated MCs (usually *KIT* D816V by qPCR), for the presence of HaT (by droplet digital PCR), and for underlying comorbidities, the most prevalent and clinically important one being an IgE-dependent allergy. When no clonal MCs and no IgE-dependent allergy (or other underlying reactive/atopic disease) is detected, the patient is either suffering from idiopathic MCAS or from a pure HaT+ MCAS. When more than one family member in such a HaT+ family fulfill MCAS criteria, the term hereditary or familial MCAS is also appropriate. When *KIT* D816V+ MCs are detected, a primary (clonal) form of

MCAS is diagnosed. This MCAS variant is also known as MMAS. In most of these patients, an underlying SM is found. In MCAS patients who are suffering from a documented IgE-dependent allergy (or another form of allergy/atopy or another reactive underlying process that can explain anaphylaxis and MCAS), a secondary MCAS will be diagnosed. In many patients with MCAS, a combined form of MCAS (mixed MCAS) is detected. These patients are at highest risk to develop life-threatening repeated episodes of anaphylaxis fulfilling all MCAS criteria. MCAS, mast cell activation syndrome; IgE, immunoglobulin E; MMAS, monoclonal mast cell activation syndrome. The dashed line divides patients' groups into those with or without a genetic predisposition.

Depending on the etiology of MCAS, 3 major variants have been defined: primary (clonal = monoclonal) MCAS, secondary (reactive) MCAS, and idiopathic MCAS (Table 3) [19–22, 47]. In patients with primary (monoclonal) MCAS, MC are (mono)clonal cells, often increase in number, and may appear hyper-reactive against IgE-dependent and/or IgE-independent triggers of anaphylaxis [19–22]. In most of these patients, MC display the *KIT* mutation D816V, and SM is diagnosed (Table 2). In a few cases with *KIT* D816V+ MCAS, the criteria to diagnose SM are not (yet) fulfilled [51, 52]. These patients are still regarded as primary MCAS, and in some of these cases, overt SM is diagnosed during follow-up. In patients with secondary MCAS, an IgE-dependent or IgE-independent allergic disease is usually identified as causative etiology [19–23]. If no underlying allergic or other reactive disease

is detected and MC are normal (polyclonal) cells, the idiopathic form of MCAS is diagnosed (Table 3; Fig. 2) [19–23].

During the past few years, more and more studies have shown that two or even three variants of MCAS can coexist in the same patient and that these patients bear the highest risk for the development of life-threatening MCAS episodes [22, 23]. For example, in patients with SM and an IgE-dependent allergy against bee or wasp venom, both the underlying SM and the underlying venom allergy may act as a trigger of anaphylaxis and thereby induce a mixed (primary + secondary) form of MCAS. Therefore, such combined (mixed) form of MCAS should always be considered in patients with severe anaphylaxis (Fig. 2) [22, 23].

In other patients, familial clustering of MCAS episodes is observed. Several of these patients are suffering from allergies and are carriers of HaT [53]. Currently, there is a discussion about the terminology of HaT+ cases fulfilling MCAS criteria. So far, the term “HaT+ MCAS” seems to be appropriate. Since the condition is based on a hereditary trait and familial clustering can occur, we are of the opinion that this form of MCAS may also be termed hereditary (or familial) MCAS when several (more than one) family members indeed fulfill all MCAS criteria (Fig. 2) [53]. The coexistence of HaT and other predisposing conditions, such as an insect venom allergy and/or mastocytosis is associated with a high risk of severe anaphylactic reactions.

Predisposing Genetic Variants and Patterns and Clonal Disease States

A number of gene variants and genetic background patterns have been associated with the manifestation or severity of atopic states and overt allergic disorders. Several of the affected genes encode proteins physiologically involved in the regulation of MC development, such as KIT, IL-4, or IL-6, the production of IgE, and/or the regulation of expression of the IgE receptor on MC, where IL-4, the IL-4 receptors, and IL-13 may play a role [54–56]. Other genes (variants) encode for proteins that are produced in MC and/or other immune cells and are involved in the regulation of vascular stability or dysfunction, such as angiotensinogen, angiotensin-converting enzymes, or chymase [8, 20, 57, 58].

Symptoms of MCA are frequently recorded in patients with a clonal MC disease [8, 19, 22, 41]. In a vast majority of these patients, a somatic mutation in the *KIT* gene, leading to ligand-independent activation of the receptor and autonomous expansion of MC, is detected and an underlying SM is found [19, 59–63]. Many of these patients suffer from MCA, and some of them even develop an overt MCAS [41, 64–69].

Several hypotheses have been raised to explain the high prevalence of MCA and MCAS in patients with *KIT* D816V+ SM. The most important etiology may be *KIT* D816V-mediated autonomous expansion of MC [70]. Indeed, the burden of MC is usually high in these cases, and the *KIT* mutation D816V is a somatic defect that is detected not only in MC but also in immature proliferating MC progenitor cells that can divide and give rise to a larger number of neoplastic MC [71, 72], whereas mature MC themselves are nonproliferating cells [73]. However, se-

vere MCA and MCAS may also be found in patients with SM and a low serum tryptase level and thus a low MC burden [74].

The mutation-mediated activation of the KIT receptor has also been discussed as a trigger of MCA [69]. However, IgE-dependent activation and releasability of *KIT* D816V-transduced ROSA cells and *KIT* D816V+ bone marrow MC obtained from patients with SM did not result in (augmented) mediator release [75]. In addition, many patients with *KIT* D816V+ SM remain asymptomatic for their lifetime or at least for many years, even if the burden of *KIT*-mutated MC is very high. Therefore, the hypothesis has been raised that *KIT* D816V+ MC stay in a form of desensitization against MCA [75], and only additional triggers of MCA may in part overcome this “desensitization status.” Indeed, in most symptomatic patients with *KIT* D816V+ SM and clear signs of MCA or MCAS, a concomitant allergy, nonallergic hypersensitivity, toxic reaction, or a hereditary predisposition is detected [26–28, 41, 64–69]. It is also worth noting that anaphylaxis has also been reported in cases with SM in the absence of *KIT* D816V or in those in whom neoplastic MC displayed other *KIT* mutations [76].

As mentioned before, HaT is a genetic trait that has been associated with an elevated basal serum tryptase concentration (most cases), an increased prevalence of SM, and an increased risk to develop severe mediator-related symptoms and MCAS in SM patients [24–28]. Interestingly, HaT is also more prevalent in patients with nonadvanced SM compared to patients with advanced SM. However, the most intriguing correlation is between HaT and the presence of severe mediator-related symptoms [26–28]. In these HaT carriers with SM and MCAS, a concomitant IgE-dependent allergy is also detected quite frequently. All in all, there seems to be a clinically relevant “high-risk complex” consisting of HaT, SM, and an IgE-dependent allergy (often against Hymenoptera venoms), and these patients apparently are at a very high risk to develop severe or even life-threatening anaphylaxis or even a combined (and most severe) form of MCAS (Fig. 2). It is also worth noting that patients with HaT appear to have slightly elevated numbers of bone marrow MC in the absence of SM [77]. Therefore, it may well be that HaT is a primary genetic factor that not only predisposes for MCA and MCAS but also for MC expansion and thereby also facilitates the development and evolution of *KIT* D816V+ SM.

There may be also other predisposing genetic variables and constellations that might play a role in the manifestation of anaphylaxis, MCA, and MCAS in patients with

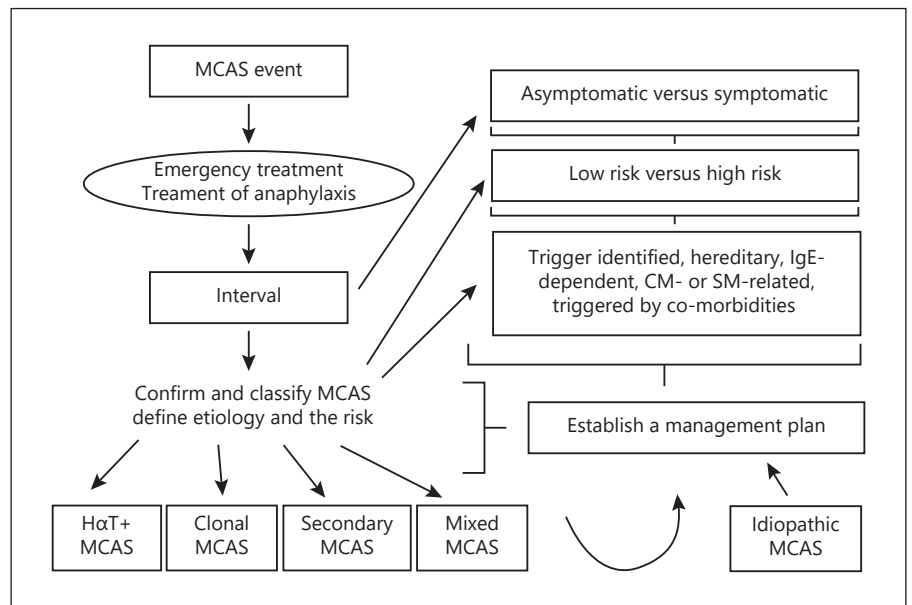


Fig. 3. Therapeutic approach to patients with MCAS. In the acute phase of an MCAS event, emergency treatment is required, and the patient is treated for acute anaphylaxis regardless of the etiology of MCAS. Rather, in most cases, MCAS criteria can only be applied in the event-free interval (when data from baseline and event-related tryptase are available). At that time, the diagnosis of MCAS is established using MCAS criteria, and the type of MCAS is determined. Then, based on the etiology, identified triggers, patient-related factors (including the genetic state), and underlying comorbidities and conditions, a comprehensive management plan is

established. In primary, secondary and mixed forms of MCAS, it is a straightforward approach to develop a treatment plan. This is not the case in patients with idiopathic MCAS. In fact, in the absence of any known etiologies or underlying conditions, it is notoriously difficult to recommend specific treatments, and the only way to proceed is to repeat all diagnostic tests and investigations and to offer symptomatic treatment and prophylactic anti-allergic drugs. Details about various treatment options (management) for patients with distinct form of MCAS are provided in the text and in Table 4 of this manuscript.

SM [78, 79]. A general atopic predisposition as well as epigenetic changes may also contribute to the development and severity of MCA and MCAS in these cases.

Comorbidities Contributing to MCA in Patients with SM and MCAS

In addition to the genetic variables discussed above, a number of comorbidities and other patient-related risk factors may contribute to the development and manifestation of MCA and anaphylaxis (MCAS) in SM. The most frequently recorded clinically relevant comorbidities are IgE-dependent allergies [19–21, 41, 64, 65]. Especially allergies against Hymenoptera (bee or wasp) venoms are well-known disorders that can cause MCA and MCAS in patients with SM [64, 65, 67, 74]. However, also other IgE-dependent and IgE-independent hypersensitivity reactions may complicate the clinical course in SM. Moreover, patients with SM may suffer from hypersensitivity

to food, alcohol, medications, physical stimuli, or stress and may sometimes even develop an MCAS during exposure [13, 80, 81]. Some of these reactions may be aggravated or facilitated by the genetic background of the patient. For example, patients with HαT or the p.C492Y variant of the adhesion G-protein coupled receptor ADGRE2 (CD312) may react to vibration and develop “vibration urticaria” [82, 83]. Chronic inflammatory disorders, auto-immune disorders, rheumatic diseases, neurologic diseases, and infectious diseases may also support MCA and may thus induce or trigger MCA and MCAS in these patients [3, 8, 9, 65]. The cytokine storm that is often detected in these cases and the related signaling cascades may support the expansion and distribution of MC in various tissues but can also support MCA [3, 8, 9]. All in all, the complexity of the etiology underlying MCA in MCAS patients and the many disease-related and patient-related cofactors are an emerging challenge in daily practice, both in diagnostic terms and also regarding optimal management.

Table 4. Personalized treatment strategies for patients with severe MCA and MCAS

Type of MCAS	Underlying diseases and etiologies	Treatment strategy to consider in patients
<i>Pure MCAS forms</i>		
Primary (clonal) MCAS	SM > CM > 1–2 SM criteria Increased MC burden Increased mediator burden	MC-reducing therapy Anti-mediator therapy, MC-stabilizing therapy
Secondary MCAS	IgE-dependent allergy Hymenoptera venom allergy Resistant IgE-dependent allergy Acute inflammation Intolerance reactions Intoxications Infections	Anti-allergic therapy Immunotherapy Omalizumab and other anti-allergic therapy Corticosteroids Symptomatic Symptomatic Anti-infective drugs
Idiopathic MCAS	Unknown Unknown	Anti-allergic drugs Symptomatic
HaT and MCAS	Familial predisposition	Anti-allergic drugs, symptomatic
<i>Mixed MCAS forms</i>		
Clonal and secondary MCAS	SM,/CM, clonal MC IgE-dependent allergy Hymenoptera venom allergy IgE-mediated and resistant Advanced SM	Anti-allergic drugs Symptomatic Immunotherapy life-long Omalizumab Cytoreductive drugs (KIT-targeting drugs) to reduce target cell burden
Primary MCAS and HaT	SM,/CM, clonal MC SSM or Advanced SM	Anti-allergic drugs Cytoreductive drugs (KIT-targeting drugs)
Secondary MCAS and HaT	IgE-dependent allergy Hymenoptera venom allergy IgE-mediated and resistant	Symptomatic Immunotherapy life-long Omalizumab

MC, mast cell(s); MCA, mast cell activation; MCAS, MCA syndrome; IgE, immunoglobulin E; HaT, hereditary alpha tryptasemia; SM, systemic mastocytosis; CM, cutaneous mastocytosis; SSM, smoldering SM.

Personalized Medicine Approaches to Address the Genetic Background, Complex Pathology, and the Comorbidities Underlying MCAS

In the past few years, accumulating data have suggested that it is important to define the co-triggering underlying etiologies contributing to severe MCA-related symptoms in patients with MCAS. In addition, accumulating evidence suggest that MCAS patients require a multidisciplinary approach and patient-specific individualized treatment [23]. In the first step, the etiology and variant of MCAS need to be defined. In many patients with mastocytosis, a combined form of MCAS (primary plus secondary) is diagnosed as these patients may also suffer from an IgE-dependent allergy, for example, an allergy against bee

or wasp venom. In some of these cases, additional predisposing conditions, such as an atopic predisposition (with elevated IgE) or HaT is documented (Fig. 2). It is worth noting that the HaT carrier status is found in nearly 20% of all cases with SM and is even more prevalent in symptomatic patients with SM (prevalence in the general population: around 5%) [26–28]. In other patients, additional underlying conditions and comorbidities, such as IgE-independent allergies, infections, or chronic tissue inflammation, may contribute to the development of MCAS episodes. Some of these coexisting conditions can be treated effectively with immunotherapy (e.g., Hymenoptera venom allergy), anti-infective drugs, or anti-inflammatory drugs. In those with massive tissue inflammation, corticosteroids may be required to suppress the inflammatory

reactions and to avoid tissue damage. All in all, detailed knowledge about the category of MCAS and the underlying etiology should provide a solid basis for establishing a personalized management and treatment plan for (almost all) patients with MCAS (Fig. 3).

As mentioned, immunotherapy against bee or wasp venom is often recommended for MCAS patients with documented Hymenoptera (bee or wasp) venom allergy (Table 4). In those with SM and a documented bee or wasp venom allergy (mixed MCAS), life-long immunotherapy is standard (Table 4) [23, 84–86]. The recommendation to treat life-long in these patients is based on the observation that discontinuation of immunotherapy may be followed by new fatal anaphylactic episodes (MCAS relapse) [87]. For patients with an extremely high risk (genetic predisposition, recurrent anaphylaxis) or resistant disease with known involvement of IgE, IgE-depleting therapy (e.g., with omalizumab) may help to avoid MCAS events and/or to keep anaphylaxis under control [88–90]. Omalizumab may also be useful in combination with other anti-allergic drugs and may also suppress adverse reactions against venom immunotherapy in patient with SM [91–93].

Regardless of the variant of SM and underlying pathologies and conditions, all patients should receive basic therapy with histamine receptor-1 (HR1) and HR2 blocker and MC-stabilizing agents as needed [18–23, 94]. In those with recurrent or resistant disease, additional corticosteroids may be required, especially when the symptoms are severe and persistent. These therapeutic maneuvers reduce the risk of occurrence of severe MCAS events. A most important and effective approach is the strict avoidance of any known or suspected triggers of anaphylaxis in these patients [19–23].

When the burden of MC is very high in SM and contributes to the severity of MCA and MCAS, MC-reducing (antineoplastic or targeted) drugs, such as cladribine (2-CdA) or novel KIT D816V-targeting tyrosine kinase inhibitors, such as midostaurin or avapritinib, may be considered as an experimental approach. This is especially recommended when MCAS events are recurrent and resistant against all conventional therapeutic maneuvers and the patient is suffering from smoldering or advanced SM. Indeed, these drugs are capable of reducing the MC burden in most patients with advanced SM, including aggressive SM and MC leukemia [95–98]. In addition, it has been shown that both drugs decrease the severity of mediator-related symptoms and improve the quality of life in these patients [95–98]. Midostaurin is also known to block IgE-mediated release of histamine from MC and basophils, which may also contribute to the clinical effi-

cacy of this drug [99]. 2-CdA has also been described to suppress MC expansion and mediator-related symptoms in patients with smoldering or advanced SM [100–103].

Depending on the overall situation, underlying etiologies, and the responses to therapy, these drugs may also be administered in combination or in sequential application, with recognition of potential drug-drug interactions and accumulating side effects. For example, complete control of MCAS has been reported in MCAS patients with H α T+ smoldering SM, drug-resistant IgE-dependent allergies, and repeated life-threatening anaphylaxis after sequential therapy with 2-CdA to reduce MC numbers and omalizumab to bring IgE-dependent reactions under control [104]. However, even omalizumab and other anti-allergic drugs may not bring anaphylaxis under control in all patients. For these cases, novel experimental therapies need to be developed.

Summary and Future Perspectives

During the past few years, accumulating evidence suggests that a complex etiology with a number of underlying genetic patterns, somatic changes, and comorbidities as well as other patient-related factors and mechanisms contribute to the clinical picture and course of MCASs. Predisposing genetic features and patterns include H α T and an atopic diathesis. KIT-activating somatic mutations in *KIT* can lead to an enormous expansion of MC and the clinical picture of SM and may thus contribute to the severity of MCAS events in affected patients. The most prevalent and significant group of comorbidities inducing or triggering MCAS events in patients are IgE-dependent allergies. Most importantly, several of these predisposing and inducing conditions can coexist in 1 patient, leading to an exceptionally high risk to develop a combined and thus more severe MCAS. Highlighting examples are SM patients suffering from H α T and/or from Hymenoptera venom allergy. The risk of life-threatening MCAS events is exceptionally high in these cases. Based on this knowledge, we recommend that all patients with MCAS are examined for the presence of contributing genetic conditions and contributing comorbidities and pathologies. As a result, the diagnosis and prognostication of patients with MCAS will improve. In addition, our improving knowledge about underlying etiologies should pave the way for designing better therapeutic algorithms and the development of personalized treatment approaches for patients with primary, secondary, or combined MCASs.

Conflict of Interest Statement

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Author Contributions

All the authors contributed equally to the project and article by reviewing the literature, by developing ideas and concepts, and by formulating expert statements.

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