

Anaphylaxis and Mast Cell Disorders



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KEYWORDS

- Anaphylaxis • Mastocytosis • Mast cell hyperreactivity • D816 V mutation
- Tryptase • Mast cell activation syndromes • Hereditary alpha-tryptasemia

KEY POINTS

- Patients with mastocytosis have a high risk of developing severe anaphylaxis, not only when suffering from venom allergy but also in the absence of a clear trigger/allergy.
- The severity and frequency of anaphylactic reactions in patients with mastocytosis may depend on hyperreleasability of mast cells due to their inherent state of hyperreactivity, and due to the potential influence of occult or overt IgE-dependent allergies.
- Comprehensive management of patients with mastocytosis with anaphylaxis can be complex and requires special knowledge about disease pathogenesis and special considerations in prophylactic measures; patient care should therefore be implemented in specialized centers or in close collaboration with experts.

INTRODUCTION

Mast cells (MCs) are granulated, tissue-fixed effector cells that reside in almost all vascularized tissues.^{1,2} The multifunctional capacity of MCs originates from their ability to detect triggers of internal or external stress or danger, which leads to the release of a spectrum of mediators.^{3,4} Both the number of MCs and their activation in the tissue increase with inflammation, but it remains elusive how the MC reactivity is regulated.

MCs are well known for their role as the effector cells of immediate-type hypersensitivity reactions; however, they also play a crucial role in the pathogenesis of MC disorders, such as mastocytosis. MC activation may occur at the local level, such as in urticaria, or systemically with clinical signs and symptoms of anaphylaxis.^{3,5,6} Although IgE-mediated reaction, through the cross-linking of IgE molecules bound to the MC surface by FcεRI receptors, is thought to be the most common pathway, non-IgE-mediated mechanisms involving activation of complement C3a/C5a

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receptors^{6,7} or the Mas-related G protein receptor-X2 (MRGPRX2) have also been proposed.⁸ Upon activation, MCs release granule-stored and newly formed cell membrane-derived lipid mediators and cytokines into the extracellular space. These mediators include histamine, proteases, proteoglycans, eicosanoids, and cytokines such as tumor necrosis factor- α .^{9,10} Blood basophils may also participate in allergic and other inflammatory reactions in the same way as MCs^{11,12}; nevertheless, not all hypersensitivity reactions involve both cell types, even if the reaction is systemic. Notably, some of the mediators involved in anaphylactic reactions are produced and released primarily by MCs, but not by basophils. Inappropriate release of MC mediators causes the so-called mast cell mediator-related symptoms.

ANAPHYLAXIS

Anaphylaxis can be defined as an acute, severe, systemic hypersensitivity reaction and represents an example of excessive MC activation resulting in an abundant release of various mediators (see definition of anaphylaxis in Adriana G. Bagos-Estevez and Dennis K. Ledford's article, "[Anaphylaxis: Definition, Epidemiology, Diagnostic Challenges, Grading System](#)," in this issue). Anaphylaxis concurrently affects multiple organ systems and presents with a broad array of symptoms and signs. Data about the prevalence and incidence of anaphylaxis are limited and often inconsistent.^{13–17} It is, however, widely accepted that anaphylaxis is a relatively rare condition. Studies from the United Kingdom indicate an increase in hospital admissions due to anaphylaxis over the last 2 decades.¹⁸ The diagnosis of anaphylaxis is based on a constellation of different signs and symptoms, and the current diagnostic criteria require concurrent occurrence of a minimum of 2 organ systems that generally include the cutaneous, gastrointestinal (GI), respiratory, and cardiovascular systems^{19,20} (**Table 1**). For information regarding the grading system, epidemiology, and differential diagnosis of anaphylaxis, see Adriana G. Bagos-Estevez and Dennis K. Ledford's article, "[Anaphylaxis: Definition, Epidemiology, Diagnostic Challenges, Grading System](#)," in this issue and Motosue and colleagues' article, "[Anaphylaxis: Epidemiology and Differential Diagnosis](#)," in this issue.

Thus, anaphylaxis presently remains a clinical entity and its understanding for an allergist remains limited with respect to factors determining severity and underlying intracellular effector mechanisms. Anaphylaxis comprises a heterogeneous group of conditions regarding the nature and route of exposure to triggers, organ involvement, severity, and time course. Hence, it would be reasonable to consider anaphylaxis as a syndrome, in which different phenotypes and endotypes may be described instead of defining the condition as a "single clinical entity." For instance, food-induced systemic reaction is a leading cause of anaphylaxis in children, whereas venom- or drug-induced reactions account for most adult cases.^{16,21–23} The distinctions not only are limited to triggers but also are applicable to the clinical manifestations. In addition, mortality occurs mostly in adult patients due to cardiovascular failure, whereas this manifestation is rare in children.^{24,25}

From this perspective, severe anaphylaxis (SA) seems to be a distinct anaphylaxis phenotype, because all these observations cannot be merely explained by a random phenomenon. At present, the clinical and biological features of SA are not yet well characterized, although these patients usually present with hypotension and/or loss of consciousness. It is therefore crucial to gain deep insight into the underlying mechanisms. In this regard, subjects with MC activation disorders (MCAD), including mastocytosis, provide a unique disease model to investigate specific features of SA, because the existing evidence indicates a strong association between these 2 conditions.^{26–28}

Table 1
Criteria for the diagnosis of anaphylaxis and related disorders of severe mast cell activation

Disorder	Diagnostic Criteria
Anaphylaxis	Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:
1	Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, itching or flushing, swollen lips-tongue-uvula) AND at least one of the following:
A	Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak flow, hypoxia)
B	Cardiovascular compromise (eg, hypotension, syncope, collapse, incontinence)
2	Two or more of the following that occur rapidly after exposure to a <i>likely allergen</i> for that patient (minutes to several hours):
A	Involvement of the skin or mucosal tissue
B	Respiratory compromise
C	Cardiovascular compromise
D	Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3	Hypotension after exposure to a <i>known allergen</i> for that patient (minutes to several hours)
SM	Diagnosis requires presence of major and 1 minor criterion or presence of 3 minor criteria in extracutaneous organ biopsy specimens, preferably bone marrow:
Major criterion	Multifocal aggregates of MCs (≥ 15 MCs per cluster) in biopsy sections
Minor criteria	
1	In MC infiltrates in extracutaneous biopsy sections, $>25\%$ of the MCs (CD117+) are spindle shaped or have atypical morphology
2	Presence of an activating <i>KIT</i> mutation at codon 816, generally D816V, in bone marrow, blood, or other extracutaneous organ(s)
3	Detection of aberrant MC clones expressing CD117 with CD25 and/or CD2 in bone marrow or blood or another extracutaneous organs
4	Baseline serum tryptase persistently exceeds ≥ 20 ng/mL
MMAS	Diagnosis requires presence of one or 2 minor criteria of SM:
1	Presence of an activating <i>KIT</i> mutation D816V, in bone marrow, blood, or other extracutaneous organ(s) AND/OR
2	Detection of aberrant MC clones expressing CD117 with CD25 in bone marrow or blood or another extracutaneous organ(s)
MCAS	Three criteria are required to fulfill MCAS diagnosis:
1	Severe, episodic symptoms that are attributable to MC activation with concurrent involvement of at least 2 organs including skin, cardiovascular, gastrointestinal, and upper/lower respiratory systems
2	An event-related increase in serum tryptase above the individual's sBT according to formula ($\geq \text{sBT} + 20\%$ of sBT + 2 ng/mL)
3	Appropriate response to drugs directed against MC activation or effects of MC mediators to reduce/suppress symptoms

Abbreviations: MCAS, mast cell activation syndromes; MMAS, monoclonal mast cell activation syndrome; sBT, serum baseline tryptase; SM, systemic mastocytosis.

Data from Refs. ^{19,20,30,31,37,38}

MAST CELL ACTIVATION DISORDERS

MCAD refer to a heterogeneous group of conditions that may be caused by an increased number of MCs and/or hyperactive MCs.²⁹ These disorders can vary in severity, but common symptoms include often severe reactions to insect stings, and in rare cases to foods or drugs. MCAD comprise clonal (eg, mastocytosis) and nonclonal (idiopathic) variants.²⁹ Clonal MC disorders (CMD) are well-characterized by intrinsic MC defects, including *KIT* mutation D816V, and/or expression of aberrant MC receptors, which may cause a “hyperactive” state of MCs leading to excessive release of mediators. Fig. 1, schematically illustrates the wide spectrum of disorders related to MC activation.

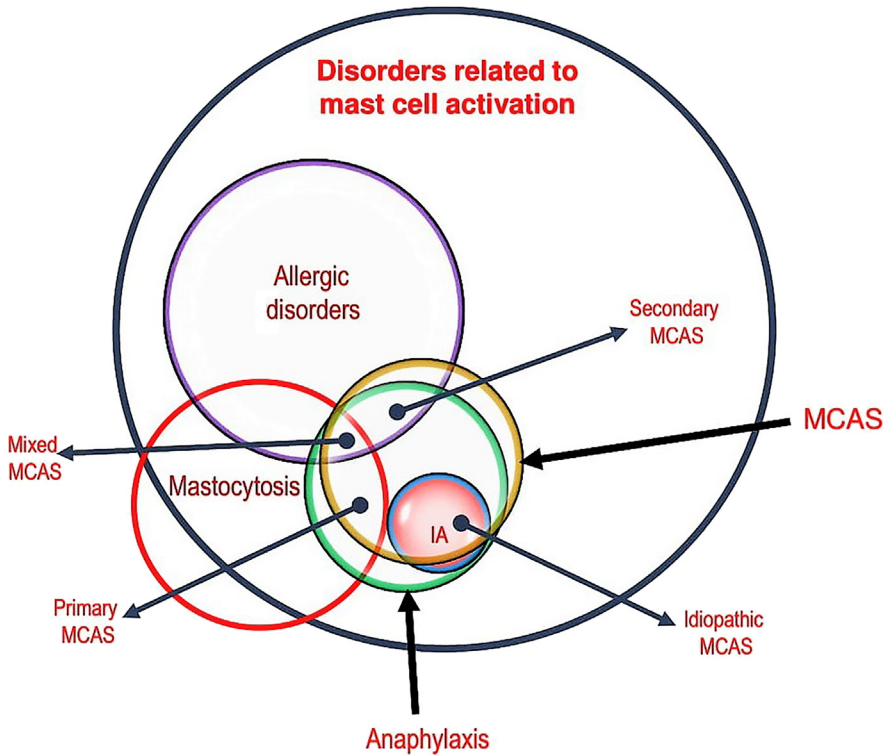


Fig. 1. Spectrum of disorders manifested by mast cell activation. These disorders encompass a broad and heterogeneous group of conditions that can range from very rare (eg, MCAS) to very common (eg, allergic disorders), some of which have an increased number of MCs and/or hyperactive MCs in various organs. It is essential to obtain accurate diagnosis due to the substantial overlapping in clinical presentation of these conditions. Please see the text for further discussion. MCAS, mast cell activation syndromes; IA, idiopathic anaphylaxis.

Mastocytosis

Mastocytosis is characterized by excessive accumulation, proliferation, and activation of abnormal MCs in several organs, including the skin, bone marrow, and GI tract.^{30,31} The World Health Organization (WHO) introduced a classification of mastocytosis into 2 main groups: cutaneous mastocytosis (CM) and systemic mastocytosis (SM) involving at least 1 extracutaneous organ.³⁰ SM has been classified into several

subgroups, with more than 85% of affected subjects having indolent SM (ISM) with a good prognosis (Box 1). The remaining 15% of affected subjects have more aggressive variants of the disease with a poor prognosis. According to the WHO diagnostic criteria, the diagnosis of SM requires the existence of a major and a minor criterion or 3 minor criteria on extracutaneous biopsy materials, most commonly from the bone marrow^{30,31} (see Table 1). The incidence and prevalence of mastocytosis are unknown, but evidence suggests that it is a rare condition. In recent studies, the prevalence of ISM is estimated to be 9.6 to 13 in 100,000 and the incidence for all subtypes of SM is predicted to be 0.89 per 100,000 per year.^{32,33}

The clinical picture of SM is protean, ranging from asymptomatic disease to a highly aggressive course with multisystem involvement. In patients with ISM, symptoms may be acute or chronic and result from the local or remote effects of excess mediator release from MCs, such as histamine, proteases, leukotrienes, and prostaglandins. Exogenous and endogenous triggers include physical exertion, cold, heat, insect venoms, consumption of alcohol, infections, nonsteroidal anti-inflammatory drugs (NSAIDs), and emotional stress. Specific triggers vary greatly among patients. Individual patients often present a variable and changing pattern of symptoms. These so-called MC mediator-release symptoms and signs include flushing, pruritus, palpitations, dizziness, hypotension, syncope, breathing difficulties, abdominal pain, nausea, vomiting, diarrhea, headache, sweating, lethargy, fatigue, impaired concentration, irritability, anxiety, depression, arthralgia, myalgia, and osteoporosis.³⁰ Not all patients experience all these manifestations; however, a history of flushing is a cardinal symptom. In addition, some subjects may experience isolated symptoms, whereas others develop a constellation of signs and symptoms resembling an anaphylaxis, which can be life threatening (ie, anaphylactic shock).^{26,28} Typically, patients suddenly feel very warm and then experience palpitations, dizziness, and a decrease in blood pressure due to systemic vasodilatation that often leads to syncope.³⁴ Acute attacks may be brief or prolonged, but duration is usually 15 to 30 minutes.³⁴ Patients often experience severe fatigue lasting around 24 hours following the spells.³⁴

There are also subjects with advanced SM, including aggressive SM, SM with associated hematologic neoplasm, and MC leukemia. Interestingly, the occurrence of anaphylaxis due to the excessive release of MC mediators in these patients is less common compared with that in patients with ISM.

Box 1

WHO classification of mastocytosis 2016^a

- Cutaneous mastocytosis (CM)
 - Maculopapular CM (MPCM) = Urticaria pigmentosa (UP)
 - Diffuse CM
 - Mastocytoma of skin
- Systemic mastocytosis (SM)
 - Indolent SM
 - Smouldering SM
 - SM with associated hematological neoplasm (AHN)^b
 - Aggressive SM
 - Mast-cell leukemia

^aAdapted from^{30,31}.

^bThe previous term *SM with clonal hematologic non-mast cell-lineage disease*.

Monoclonal Mast Cell Activation Syndrome

Recently, a novel variant of clonal MCAD has been introduced, the so-called monoclonal mast cell activation syndrome (MMAS).^{35,36} These patients are also mainly characterized by recurring episodes of anaphylaxis with hypotension and syncope and have clonal MCs expressing the D816V *KIT* mutation and/or CD25+ aberrant surface markers. However, they do not fulfill the WHO criteria for SM diagnosis and lack typical skin changes of mastocytosis (Table 1).^{35,36}

WHY IS THE RISK OF SEVERE ANAPHYLAXIS INCREASED IN MAST CELL DISORDERS?

The likelihood of MCs to secrete mediators, also known as “releasability” in the context of systemic MC activation and anaphylaxis, depends on several factors including the underlying primary disease.^{37,38} Greater severity correlates with the higher burden or number of involved MCs, and the cellular activation level, for example, “hyperactivated” state.^{37,38} These factors together result in an increased releasability of MC mediators. There are some additional factors, including level of expression of activated receptors and/or signaling molecules on MCs, genetic predisposition (eg, genetic polymorphisms in IL-10 or IL-13), copy number of the tryptase gene, route of allergen exposure (eg, parenteral route) and type of triggering allergen (eg, insect venom), level of allergen-specific IgE, triggering cofactors, hormonal influences, and the presence of comorbid conditions^{38–40} (Box 2). Such activation processes culminate in degranulation and release of preformed and newly synthesized membrane lipid mediators, such as histamine, tryptase, prostaglandins, and proinflammatory cytokines. Measurement of acute serum total tryptase is the current gold standard laboratory test to confirm systemic MC activation.

Subjects with mastocytosis, for instance, have a high risk of developing severe, life-threatening anaphylaxis; this may depend on hyperreleasability of MCs in these subjects due to their inherent state of hyperreactivity, often associated with occult or overt IgE-dependent allergies.^{37,38} Chronically activated KIT receptor in mastocytosis may be responsible for the hyperreactivity in MCs. Indeed, in almost all subjects with SM, MCs exhibit the *KIT* D816V mutation, and the KIT ligand stem cell factor augments IgE-dependent mediator release in normal MCs.³⁴ However, not all patients with SM bearing the *KIT* D816V mutation develop anaphylaxis. Therefore, additional

Box 2

Potential factors associated to severe mast cell activation

- Increased number of mast cells involved in the reaction
- Increased *releasability* of mast cells
- *Hyperreactive* state of mast cells
- Increased copy number of tryptase gene (ie, hereditary alpha-tryptasemia)
- Presence of cofactors
- Type of allergen
- Route of allergen
- Presence of comorbidities (eg, cardiovascular)
- Gender (male)
- Increased age

genetic polymorphisms or mutations in MC signaling components, other than the activating *KIT* D816V mutation, may contribute to MC dysregulation and the predisposition for anaphylaxis.⁴¹

Hereditary Alpha-Tryptasemia

Hereditary alpha-tryptasemia (H α T) is another modifying factor that may influence the prevalence and severity of anaphylaxis. H α T is a recently identified autosomal dominant genetic trait that is characterized by excess copies of alpha-tryptase gene, *TPSAB1*.^{42,43} Individuals with H α T may have slightly increased numbers of MCs in bone marrow and GI biopsies, and serum baseline tryptase (sBT) levels are typically greater than 8 ng/mL (often ≥ 10 ng/mL).⁴³ However, they generally do not have increased urinary secretion of other MC mediators, such as prostaglandins and histamine metabolites. H α T is found in approximately 6% of the general population, and there is no consistent clinical phenotype associated with H α T.^{44,45} The risk for severe spontaneous and/or insect venom-triggered anaphylaxis in H α T subjects was reported to be increased.^{46–48} It is also reported that increased germline copies of α -tryptase are associated with increased severity of venom anaphylaxis and idiopathic anaphylaxis (IA) in SM.⁴⁸ Thus, H α T may confer an increased risk for SA, which is independent of the presence of concomitant CMD. However, to date, no studies have shown that MCs in patients with H α T are hyperreactive. In addition, the prevalence of H α T among patients with allergies is the same as that among unselected controls.⁴⁴ Therefore, these findings related to H α T need to be confirmed in larger cohorts.

CHARACTERISTIC OF ANAPHYLAXIS IN PATIENTS WITH CLONAL MAST CELL DISORDERS

Distinct features of SA in subjects with SM are the profile of eliciting triggers as well as the clinical course of reactions.

The cause of anaphylaxis in SM may vary; however, Hymenoptera venom is the most common elicitor.^{26,27,49} There is a correlation between elevated sBT levels and the severity of systemic reactions to Hymenoptera stings.⁵⁰ In a study analyzing 226 patients presenting with anaphylaxis to an emergency care setting, SM was diagnosed in 7.7% of adults and stings from flying insects were the triggers in half of these subjects.⁵¹ Another study reported a 28% overall prevalence of venom-induced anaphylaxis (VIA) among 122 patients with SM, which is clearly higher than in the general population.²⁷ Interestingly, VIA may be the presenting symptom that may lead to the diagnosis of SM. In this regard, one large study reported that approximately 10% of 379 subjects with systemic reactions to Hymenoptera sting had elevated sBT levels (≥ 11.4 ng/mL), and most of these subjects had SM or MMAS diagnosed by bone marrow biopsies.⁵² Many such patients have evidence of venom-specific IgE in blood, although specific IgE levels may be lower compared with the nonmastocytosis venom-allergic population⁵³; this could possibly be due to the binding of IgE onto the increased numbers of MCs, making it less available to be detected in the serum. Notably also, skin prick test reactions to venom extract in SA may be diminished in size or even absent.⁵⁴

Drug- or food-induced reactions were also reported as an elicitor of anaphylaxis in SM^{28,55}; however, most of those reactions remain patient reported and unconfirmed. Therefore, interpretations of these data should be made with caution due to the lack of reliable confirmatory in vitro tests and the absence of provocation tests. There are occasional case reports of patients with allergy to foods or preservatives.⁵⁶ Another case report presented a patient with more than 10 SA episodes

after eating meat, where a provocation test with pork resulted in delayed SA with only low levels of specific IgE to meats and galactose- α -1,3-galactose.⁵⁷ Further diagnostic workup confirmed an underlying ISM.⁵⁷ Most recently, a large, systematic study investigating food hypersensitivity and food-induced anaphylaxis (FIA) in SM subjects found that the prevalence of FIA in SM was at least 10-fold less compared with the prevalence of VIA in SM.⁵⁸ Thus cumulative clinical experience suggests that the incidence of IgE-mediated food allergy is not, or not fundamentally, increased in subjects with SM compared with that in the general population.⁵⁸ Some patients with SM complain about flushing and GI symptoms triggered by histamine-rich diets, spicy foods, and alcohol; however, these symptoms rarely progress to anaphylaxis.⁵⁸

Likewise, data on patients with drug hypersensitivity and MC disorders are scarce and literature is largely limited to case reports.⁵⁹ Remarkably, most of these cases are related to general anesthesia and radiocontrast media exposure.^{60,61} Experience suggests that some patients with SM may be at risk for severe non-IgE-mediated reactions, such as those experienced with perioperative muscle relaxants. Such risk is probably lower in patients who have tolerated previous general anesthesia and/or who have no history of anaphylaxis during anesthesia. At present, available data in the literature are scant on this topic, and it is not possible to provide clear recommendations. Some experts suggest premedicating with antihistamines and corticosteroids before anesthesia and recommend perioperative drugs with lower intrinsic MC activation properties. Furthermore, unlike VIA, drug-induced anaphylaxis (DIA) is rarely associated with undetected MC disorder in the literature. In this regard, a study investigating patients with NSAID hypersensitivity and its correlation to occult SM failed to show elevated sBT levels.⁶² Thus, it is not known whether the incidence of DIA is increased in SM because there are currently no systematic studies.

By contrast, patients with IA, that is, unexplained anaphylaxis, are more likely to have SM.^{26,55} Indeed, there is an intriguing relationship between IA and MCAD. Because CMD can be potentially misdiagnosed as IA, it is, therefore, essential to distinguish it from true IA.^{35,63} Akin and colleagues³⁵ reported the presence of a clonal MC population in 5 of 12 patients with IA in whom there were no features of urticaria pigmentosa or histologic evidence for SM on bone marrow biopsies.³⁵ Similarly, Gulen and colleagues⁶³ performed bone marrow examinations in 30 cases of unexplained SA without signs of CM and reported that 47% of these patients were subsequently diagnosed with CMD, both clonal and/or aberrant MC populations. Finally, a recent study investigated 56 subjects with more than 3 episodes/y of unexplained SA. Bone marrow (BM) examination found evidence of MC clonal disease in 14% (8 of 56).⁶⁴ The reasons for the discrepancies among these studies may be the differences in diagnostic criteria for IA and referral patterns.

Another suggestive feature of SA in patients with SM is the distinct clinical pattern and course of episodes. Patients with SM with SA frequently present with severe cardiovascular signs and symptoms including hypotensive syncope,^{26,28,49} whereas respiratory symptoms, urticaria, and angioedema are rare.⁴⁹ For instance, the occurrence of syncope/loss of consciousness has been reported to be 72% during SA among patients with SM regardless of triggers²⁶; this is also confirmed in SM with VIA.⁵³ These observations led to the development of predictive models to distinguish patients presenting with SA and underlying CMD, specifically SM and MMAS. Because the diagnosis of SM requires an extracutaneous biopsy, it may be challenging for clinicians to decide whether to pursue further evaluation in subjects presenting with SA but no other features of SM. In this regard, the Spanish

Network on Mastocytosis (REMA) proposed a scoring tool to predict high-risk patients, which is based on a combined clinical (ie, male gender and clinical symptoms of syncopal episodes in the absence of urticaria/angioedema during SA) and laboratory (elevated sBT levels of ≥ 25 ng/mL) criteria.⁴⁹ Thus, the REMA score has been used to screen patients presenting with SA but lack typical signs of CM and showed a sensitivity of 92% and specificity of 81%, regardless of the trigger.⁴⁹ A modification of the “REMA score” subsequently has been proposed as the “Karolinska score,” using a reduced sBT level of ≥ 20 ng/mL.⁶³ This modified version resulted in a better sensitivity (93%) and specificity (94%), when retrospectively applied in patients with IA.⁶³ When available, these tools should be used together with peripheral blood *KIT* D816V mutation analysis, because it is independently a strong indicator of the underlying SM.⁶⁵ Finally, further modification of previous tools was proposed—the so-called National Institute of Health Idiopathic Clonal Anaphylaxis Score—by using clinical symptoms, gender, a baseline tryptase cutoff of 11.4 ng/mL, and allele-specific polymerase chain reaction testing to detect the presence or absence of *KIT* D816V mutation in peripheral blood.⁶⁴ However, this scoring tool has not been yet validated.

MAST CELL ACTIVATION SYNDROMES

MC activation syndrome (MCAS) may be diagnosed in some patients when the symptoms are systemic and MCAS criteria are fulfilled^{37,38,66,67} (see [Table 1](#)). MCAS can be defined as a disorder of MC activation with various causes all resulting in severe, recurrent, and episodic symptoms due to systemic MC mediator release.^{37,38,66,67} Patients with MCAS often present with symptoms of anaphylaxis. However, it is noteworthy that neither all anaphylaxis fulfill diagnostic criteria of MCAS nor do all MCAS episodes reach the severity of anaphylaxis. It is also worth mentioning that MC activation can manifest as a less severe and/or chronic condition, therefore MCAS cannot be diagnosed in these patients. Thus, not all mediator-related and clinically relevant symptoms can be classified as MCAS.³⁸

Three sets of criteria are required for an MCAS diagnosis: (1) typical episodic symptoms consistent with MC activation, (2) objective laboratory evidence of MC involvement with a substantial transient increase in validated MC mediators in the serum or in the urine (preferably, an event-related increase in serum tryptase levels according to the formula $\geq 1.2 \times \text{sBT} + 2$ ng/mL within 4 hours of an acute episode), and (3) control of symptoms with MC-directed therapies.^{37,38,67} Once a diagnosis of MCAS has been confirmed, further classification is necessary. MCAS has been classified into 3 variants.^{37,38} Primary MCAS is defined by the presence of clonal MCs and includes MMAS and mastocytosis (systemic and/or cutaneous) ([Table 2](#)). Diagnosis of primary (clonal) MCAS can only be made after an extracutaneous biopsy, most often after a bone marrow biopsy.^{30,31} Clonal MCAS can present with IA.^{35,63,64} Secondary MCAS results in symptoms of MC activation through IgE- and non-IgE-mediated processes, such as food-, drug-, or Hymenoptera venom-induced SA. This variant has no evidence of a clonal MC population. Finally, idiopathic MCAS results in MC activation symptoms without a clear precipitating cause. Patients with IA are the epitome of idiopathic MCAS; therefore, it is essential to evaluate whether the patient meets criteria for IA. However, idiopathic MCAS is a broader entity and may also include patients whose episodes may not fulfill the clinical criteria of IA, such as patients presenting with concomitant skin and GI symptoms causing event-related elevation of serum tryptase.

Table 3 illustrates features of anaphylaxis in various MCADs and HxT.

THERAPEUTIC OPTIONS

Acute episodes of SA in patients with MC disorders should be treated in the same manner as other forms of anaphylaxis.^{20,68,69} Roberts and colleagues^{70,71} stressed the unique role of epinephrine in the treatment of SA in a patient with SM who was refractory to vasopressor therapy with dopamine, yet quickly improved with epinephrine. Intramuscular (IM) epinephrine is the drug of choice. Evidence suggests that treatment of systemic reactions with epinephrine prevents progression to more severe symptoms.⁶⁹ Unfortunately, epinephrine is still underutilized, whereas corticosteroids are widely used as first-line therapy despite the lack of evidence.⁷² In refractory cases of severe hypotension not responding to repeated doses of IM epinephrine, or hypotension followed by cardiac arrest, intravenous (IV) epinephrine should be given with continuous monitoring of cardiac response, blood pressure, and oxygen saturation. Supplemental high-flow oxygen and IV fluid (eg, normal saline) replacement should be administered. When cardiovascular status and respiratory function stabilize, second-line medications such as histamine receptor type-1 (HR1) and type-2 (HR2) blockers and corticosteroids are usually recommended.⁶⁸ However, the value of corticosteroids in the acute management of anaphylaxis is unclear because there is no substantial evidence to support their proposed effect on the prevention of protracted or biphasic reactions.⁷³

With regard to the long-term management and prevention of SA, measures aim to reduce the severity and/or frequency of the acute episodes. Prevention is the most important aspect, therefore all patients with mastocytosis who have a history of anaphylaxis should be prescribed self-injectable epinephrine after receiving adequate information and training on the appropriate use. Information and education should also be extended to the patient’s family and caregivers, and an action plan for the management of acute episodes should be implemented.

Although avoidance is the mainstay of the prevention of SA, there is a wide individual variation among patients with mastocytosis. Hence, the general advice to avoid all the literature-reported potential triggers for MC degranulation is not recommended; instead, a tailored management strategy is necessary.⁷⁴ When possible, patients should undergo a thorough allergy workup including allergy tests for several known/

Table 2 Classification of mast cell activation syndromes	
Variant of MCAS	Clinical and Laboratory Findings
Primary (clonal)	Clonal mast cells found a. Established SM: criteria to diagnose SM are fulfilled b. Established CM: criteria for CM are fulfilled but the criteria to diagnose SM are not fulfilled c. Neither CM nor SM can be diagnosed, but one or both of the following minor SM criteria documenting mast cell clonality found: i. <i>KIT</i> D816V or ii. CD25 expression in mast cells
Secondary	An underlying allergic, atopic, inflammatory, or neoplastic disease is found but no monoclonal mast cells are detectable (<i>KIT</i> mutation and/or CD25 expression in mast cells not found)
Idiopathic	No underlying allergy or atopy and no monoclonal (<i>KIT</i> -mutated and/or CD25+) mast cells are detectable

Data from Refs.^{37,38}

Table 3
Features of anaphylaxis in various mast cell activation disorders and hereditary alpha-tryptasemia

	SM	CM	MCAS	H α T
Risk of anaphylaxis increased?	+	+/-	+	+ in a subgroup
Clinical features	Hypotension, flushing, abdominal cramping, less urticarial, and angioedema	Variable	Not all episodes may reach the severity of anaphylaxis. Symptoms may also include urticaria and angioedema; however, it should always involve ≥ 2 organs	Variable. H α T by itself does not confer a particular clinical phenotype but is thought to amplify symptoms and severity of anaphylaxis
Markers of clonality (<i>KIT</i> D816V, CD25 on MCs)	+	+/-	+ in primary MCAS, whereas – in secondary and idiopathic MCAS	Negative in pure H α T; however, SM is detected more frequently in H α T and patients may have both conditions
Baseline tryptase	>20 ng/mL in most patients	May be normal or elevated	Normal or elevated	>8 ng/mL
Diagnosis	Bone marrow biopsy and checking for WHO criteria	Inspection of skin, Darier sign, skin biopsy	Consensus criteria (see text)	Genetic testing for TPSAB1 copy number

Table 4
Prophylactic therapy in patients with mast cell activation disorders

Drug	Indication	Proposed Mechanism of Action
Histamine receptor type-1 blocker	All patients	Blocks histamine receptor type-1
Histamine receptor type-2 blocker	Patients with gastrointestinal symptoms or those not responding to histamine receptor type-1 blocker	Blocks histamine receptor type-2
Antileukotrienes	Add-on treatment in patients with persistent dermatologic complaints who do not respond adequately to histamine receptor type-1 blocker	Blocks leukotriene receptor
Cromolyn sodium	Patients with persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting, diarrhea) and resistance to histamine receptor type-1 and type 2 blockers	Effects on various cell types including MCs; may block IgE-dependent activation of MCs
Ketotifen	In patients with idiopathic anaphylaxis and resistance to histamine receptor-type 1 blockers	Inhibits activation of MCs, inhibits histamine binding to histamine receptor type 1
Aspirin	Patients with severe, recurrent anaphylaxis	Suppresses the generation of prostaglandin D ₂ in human MCs
Glucocorticosteroids	Preventive maintenance therapy at low doses for recurrent anaphylaxis not responsive to histamine receptor blockers	Blocks mediator production and cytokine synthesis as well as mediator secretion in MCs
Allergen immunotherapy	In patients with mastocytosis in whom venom allergy is detected, lifelong immune therapy is generally recommended	Effects on various cell types including MCs, and aids development of venom-specific immune tolerance
Omalizumab	Patients with severe, recurrent anaphylaxis	IgE depletion and hyposensitization of MCs through downregulation of nonspecific IgE receptors

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Table 4
(continued)

Drug	Indication	Proposed Mechanism of Action
Interferon-alpha	Generally recommended in patients with aggressive SM but has also been shown to control severe MC activation episodes	Suppresses mast cell function, including histamine release
Cladribine	Patients with aggressive variant of SM and severe, life-threatening anaphylaxis	Causes apoptosis in MCs independent of the presence of the common D816V <i>KIT</i> mutation
Midoausttrin	Patients with aggressive variant of SM and in certain cases, indolent SM with severe, life-threatening anaphylaxis	Blocks <i>KIT</i> D816V activation and MC proliferation in SM and also inhibits IgE-dependent activation and mediator secretion in MCs
Avapritinib	Patients with aggressive variant of SM and in certain cases, indolent SM with severe, life-threatening anaphylaxis	Selectively inhibits <i>KIT</i> exon 17 mutants, including <i>KIT</i> D816V

potential triggers to assess for potential culprit agents. In addition, an allergist evaluation can be used as guidance to map out patients' individual trigger profile to avoid relevant food, medication, and inhalational triggers of MC activation. For instance, eliminations of histamine-rich diets or avoidance of certain drugs including NSAIDs is not routinely recommended. In contrast, Hymenoptera stings seem to be the most frequent cause of anaphylaxis in adult patients with mastocytosis.²⁶ Thus, those with sting anaphylaxis who are sensitized to Hymenoptera venom should be recommended lifelong venom immunotherapy, which reduces recurrent anaphylaxis risk with stings.⁵³ At present, there is no consensus among experts whether to prescribe epinephrine to all patients diagnosed with mastocytosis or to prescribe it only to those with a history of anaphylaxis or who are at increased risk for anaphylaxis. This issue has been discussed in a recent study, wherein a risk assessment tool to predict occurrence of anaphylaxis in patients with mastocytosis was developed.²⁷ This tool may facilitate the determination of "correct" patients with mastocytosis who need epinephrine autoinjectors.

There are currently no randomized studies to show which prophylactic therapy options are superior in mastocytosis. A stepwise approach should therefore be considered in all patients⁷⁴ (Table 4). The first step includes HR1 blockers. Doses can be adjusted individually, and doses up to 4 times higher than the recommended doses can be used similar to those in patients with chronic urticaria. In the same manner, HR2 blockers, antileukotrienes, oral cromolyn, and corticosteroids can be additionally given in unresponsive patients. If the combination therapies are ineffective, omalizumab, which is a humanized monoclonal antibody that specifically binds to free IgE, can be used. Omalizumab has been shown to diminish the frequency of anaphylactic episodes in anecdotal reports and case series with varying success.^{63,75,76}

Nevertheless, there are presently no randomized, placebo-controlled studies to recommend omalizumab in routine use.

Although it is generally assigned for patients with aggressive SM, in rare, refractory cases, cytoreductive or immunomodulatory therapy including interferon-alpha 2b⁷⁷ and cladribine (2-CDA)⁷⁸ was historically reported to be beneficial in controlling mediator-related symptoms. Current first-line cytoreductive therapy options include tyrosine kinase inhibitors (TKIs) targeting the MC growth receptor KIT. A recent study provided initial evidence that midostaurin, in addition to reversed organ damage and decreased splenomegaly and bone marrow MC burden in patients with advanced SM,⁷⁹ was found to improve mediator-related symptoms and quality of life, suggesting that the drug may also be useful in patients with ISM suffering from severe mediator-related symptoms resistant to conventional therapies.^{80,81} Avapritinib is another novel TKI that selectively inhibits *KIT* D816V.⁸² Both midostaurin and avapritinib are currently approved for treatment of advanced SM. A recent phase 2 study reported symptom reduction and MC cytorreduction with avapritinib in patients with ISM.⁸³ Additionally, prompt resolution of recurrent anaphylaxis with the addition of avapritinib was described in a patient with SM-AHN.⁸⁴ However, the effects of TKIs on anaphylaxis remain to be explored.

SUMMARY

Anaphylaxis is an important feature of patients with MC disorders. Hence, the presence of underlying CMD should be strongly suspected in patients with VIA as well as patients with recurrent IA; in particular, when these episodes present with severe hypotensive syncope. A bone marrow examination should be considered if the sBT level is elevated (≥ 11.4 ng/mL) and/or if the peripheral blood *KIT* D816V mutation is present.

Appropriate treatment with IM epinephrine remains underutilized in most cases, despite increased awareness and recognition of anaphylaxis. Expanding knowledge on the presentation and triggers of anaphylaxis among patients with mastocytosis, their relatives, and health care providers will improve its recognition and management and increase patient safety. Moreover, a better understanding of the pathogenesis of SA by exploring the intrinsic changes in MCs of patients will provide important insight into its long-term management. Further research may lead to identification of novel biomarkers⁸⁵ to distinguish patients with SA as well as development of new drugs targeting intracellular MC activation mechanisms and mediators.

CLINICS CARE POINTS

- The presence of recurrent hypotensive episodes and/or syncope without urticaria and/or angioedema and/or respiratory symptoms during anaphylaxis increases the odds of underlying CMD.
- Patients with Hymenoptera VIA and elevated baseline serum tryptase level should be investigated for the presence of mastocytosis; particularly if peripheral blood *KIT* D816V mutation is present.
- H₂T is a genetic trait and may confer an increased risk for SA, which is independent of the presence of concomitant CMD.
- MCAS may be diagnosed when the symptoms due to MC mediator release are severe, recurrent, and systemic, and MCAS criteria are fulfilled. An event-related increase in sBT is critical to diagnosis.

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