

Mastocytosis and Anaphylaxis



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KEYWORDS

- Mastocytosis • Mast cell activation syndrome • Anaphylaxis • Risk factors
- Triggers • Hymenoptera venom anaphylaxis • Drug-induced anaphylaxis

KEY POINTS

- There are two major forms of indolent systemic mastocytosis associated with anaphylaxis: the classical form with mastocytosis in the skin, and a form without skin lesions becoming apparent only through the occurrence of anaphylactic reactions.
- Anaphylactic reactions in mastocytosis mostly are associated with Hymenoptera stings, but also may be occasionally labeled idiopathic anaphylaxis or triggered by food or drugs.
- In children anaphylaxis is uncommon, mostly idiopathic, and manifests normally during active blistering episodes in those with extensive skin involvement and high serum, whereas adults with systemic mastocytosis carry a 20%–50% risk for anaphylaxis, but with less defined risk factors.
- Because mastocytosis is a well-recognized basis for anaphylaxis, emergency preparedness, including availability and use of emergency medications and, if indicated, life-long venom immunotherapy, is necessary.

INTRODUCTION

Mastocytosis (MC) is a proliferative disorder of hematopoietic mast cell progenitors,¹ which leads to an expansion and accumulation of excessive numbers of mast cells in one or more organs, such as skin, bone marrow, gastrointestinal tract, liver, and spleen.^{1,2} The basis of the disease is an activating mutation in the mast cell growth receptor KIT, a protein tyrosine kinase receptor, most commonly a point mutation with exchange of aspartic acid to valine in codon 816 (D816V).³ More than 80% of all patients with systemic mastocytosis (SM) carry the D816V mutation.⁴

Whereas in most children only the skin seems to be involved (cutaneous MC [CM]), in adults, other organs are also affected (SM). To diagnose SM, according to the World

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Health Organization, several criteria have to be fulfilled. In detail, there are one major and four minor criteria for SM (**Box 1**), of which one major and one minor or three minor criteria are required for diagnosing SM.^{2,5}

The overall prevalence of SM in all adults with MC has been reported to be more than 95%.^{6,7} In adult SM, there is a subfraction of patients without presence of skin lesions. Comparing these patients with and without MC in the skin (MIS) there is a male predominance and history of insect-sting anaphylaxis in those without MIS.⁸ A study, for which patients with classical skin lesions and patients with insect-sting or idiopathic anaphylaxis were recruited, showed almost equal numbers of patients with indolent SM (ISM) with and without skin lesions.⁹

SM is subdivided into different clinical forms according to aggressiveness and prognosis. The most common form (90%–95% of all patients) is ISM. Rare advanced forms are SM with an associated hematologic non–mast cell disorder, aggressive SM and mast cell leukemia.¹⁰ The cumulative probability of disease progression in patients with ISM is low (calculated to be 1.7% in 10 years) and patients with ISM carry a normal life expectancy.⁷

Anaphylaxis is a systemic or generalized life-threatening and potentially fatal systemic hypersensitivity reaction.¹¹ Clinically, criteria for anaphylaxis have been defined.¹² Typically, it occurs after contact to a known allergen (eg, peanut ingestion) and involves at least two out of the four organ systems: skin (eg, flush, urticaria, angioedema), gastrointestinal tract (eg, abdominal pain, nausea, diarrhea), pulmonary system (eg, wheezing, dyspnea), and cardiovascular system (eg, hypotension, shock).¹²

In addition to patients with SM, there are patients with anaphylaxis that carry clonal mast cells expressing the D816V KIT mutation, but that do not meet enough criteria to diagnose MC. This condition has been named monoclonal mast cell activation syndrome (MMCAS).^{13,14}

EPIDEMIOLOGY
Prevalence of Mastocytosis

In 1997 it was calculated that 1 in 1000 to 8000 new patients in dermatology outpatient departments may have some form of MC.¹⁵ More recent studies found a prevalence of ISM of 9.6 to 13 in 100,000 people and an incidence for all subtypes of SM of 0.89 per 100,000 per year.^{16,17}

Box 1
Criteria for the diagnosis of systemic mastocytosis

Major criterion

- Multifocal dense aggregates of ≥15 mast cells in bone marrow and/or other extracutaneous tissues

Minor criteria

- Morphologically atypical mast cells in smears of biopsy sections of bone marrow or other extracutaneous organs
- Aberrant expression of CD25 and/or CD2 by mast cells in the bone marrow
- D816V KIT mutation in bone marrow, blood, or other extracutaneous organs
- Serum tryptase levels >20 µg/L

Prevalence of Atopy and Allergy in Mastocytosis

Smaller studies have reported that the prevalence of atopy in patients with MC is similar to that of the general population.^{18,19} In addition, a comparison of prevalence rates of IgE-mediated allergy among patients with MC and in the general population has shown no significant difference.²

Prevalence of Anaphylaxis in General Population

The general prevalence of anaphylaxis can only be estimated using data from different studies. One study based on a survey of 1000 US citizens selected at random suggests that the lifetime risk of systemic anaphylaxis may be at least 1.6%.²⁰ A more conservative systematic review has estimated a cumulative lifetime prevalence of 0.3% and the incidence to be about 5 per 100,000 person years.²¹

Prevalence of Anaphylaxis in Patients with Mastocytosis

In children with MC, the percentage of anaphylaxis has been reported to be between 6%¹⁹ and 9%.²² In adults, the cumulative prevalence of anaphylaxis is much higher, estimated to be 22%,¹⁹ 43%,²³ and 49%²² in different study populations, which may be roughly 100-times as much as in the general population. The overall risk for anaphylactic reactions is increased for patients with SM compared with patients with MC limited to the skin.²² Anaphylaxis also seems to occur more often in patients with ISM without cutaneous involvement.^{2,22,23} This, however, is no surprise, because the symptom leading to the diagnosis of SM in most patients without skin involvement is anaphylaxis, whereas skin lesions are the leading manifestation in those with MIS and the prevalence of anaphylaxis in this group is lower than 50%.

According to the previously mentioned prevalence rates, the cumulative lifetime prevalence of MC together with anaphylaxis in adults may be estimated to be between 0.002% and 0.006%.

RISK FACTORS FOR ANAPHYLAXIS IN PATIENTS WITH MASTOCYTOSIS

In one study in children with MC, the most common systemic symptoms were diarrhea and abdominal pain, whereas anaphylaxis was only present in 1.5%.²⁴ In addition to the number of skin lesions, the number of skin symptoms, such as itching, blistering, and flushing, were significant predictors of the number of systemic symptoms, showing a linear correlation.²⁴ The extent and density of skin lesions and higher serum tryptase values have also been identified as risk factors for anaphylaxis in children (**Table 1**).²² Moreover, it was shown that diffused CM, the most severe form of CM, is a risk factor for more severe anaphylaxis.²⁵

Another study with 111 children suffering from MIS, which was designed to find predictors for severe mast cell activation episodes mostly resembling anaphylaxis, showed that all 12 children with severe symptoms who required hospitalization had extensive cutaneous disease, more than 90% of the body surface area involved, and significantly higher levels of serum tryptase compared with the other children without such severe reactions.²⁶ In addition, blistering episodes seemed to be a risk factor for hospitalization.²⁷ Thus, severe systemic symptoms often fulfilling the criteria for anaphylaxis in children with MIS are likely to develop in those patients with a severe skin involvement with MC lesions, high serum tryptase levels, blistering episodes, and diffused CM, whereas the risk in the remainder seems low.

Anaphylaxis in adults was more common in those with SM than in patients with CM.²² In patients with SM and MIS, the extent and density of skin involvement was not associated with a higher risk of anaphylaxis.^{22,23,28} Baseline serum tryptase has

Table 1 Possible risk factors for anaphylaxis in patients with mastocytosis			
Patient Group	Risk Factor	Outcome	Study
Children	Extent and density of skin lesions	Anaphylaxis in those with extent >45% and density >15%	Brockow et al, ²² 2008
	Serum tryptase	Significantly elevated in patients with anaphylaxis Correlation with severity	Brockow et al, ²² 2008 Alvarez-Twose et al, ²⁶ 2012
	Skin involvement >90%	Risk factor for hospitalization ^a	Alvarez-Twose et al, ²⁶ 2012
	Blistering	Risk factor for hospitalization ^a	Brockow et al, ²⁷ 2012
	Diffuse cutaneous mastocytosis	Risk factor for hospitalization ^a	Alvarez-Twose et al, ²⁶ 2012
Adults	Extent and density of skin lesions	Not significant	Brockow et al, ²² 2008 Gülen et al, ²³ 2014
	Serum tryptase	Elevated in patients with anaphylaxis (high overlap)	Brockow et al, ²² 2008
	Form of systemic mastocytosis	Mostly in indolent systemic mastocytosis	Gülen et al, ²³ 2014
	D816V allele burden	No difference	Broesby-Olsen et al, ³¹ 2013

^a Hospitalization because of severe mast cell activation episodes.

been reported to be higher in those with as compared with those without anaphylaxis, however, with a large overlap.²² Male sex, tryptase levels greater than 25 ng/mL, anaphylaxis with cardiovascular symptoms (eg, dizziness, syncope) in the absence of urticaria or angioedema, and anaphylaxis to Hymenoptera venom have been described as indicators for MC in unselected patients with anaphylaxis.²⁹ The correlation between the risk of anaphylaxis and serum tryptase values does not seem to be linear. The prevalence of Hymenoptera venom allergy in adults was rising with basal serum tryptase levels up to a peak of around 28 ng/mL and decreasing with higher levels.³⁰

The highest risk for anaphylactic reactions comes with the diagnosis of ISM.^{23,28} Surprisingly, there is no evidence that anaphylaxis is more common in patients with more advanced SM (eg, mast cell leukemia, aggressive SM). On the contrary, in our experience it seems to be less common. Furthermore, the allele burden of KIT D816V mutation measured by quantitative real-time polymerase chain reaction was not different between adults with or without anaphylaxis.³¹

PATHOPHYSIOLOGY

The tyrosine kinase receptor KIT and its ligand stem cell factor controls differentiation and proliferation of mast cells.³² In MC, mast cells carrying an activating D816V mutation are a basis for the disease. The mutation causes a ligand-independent activation of the receptor, leading to expansion of the mast cell population.³ It has been speculated that these cells also may be hyperactive to external triggers, such as

allergens, which may result in a lower threshold for anaphylaxis. This, however, has not yet been proven. In addition, because MC is associated with an increased number of body mast cells, that is, a higher number of potential effector cells for immediate-type allergies, this could result in potentially higher mediator release and more severe symptoms of anaphylaxis (Fig. 1).

CLINICAL FEATURES

Anaphylaxis in patients with MC principally presents with the same symptoms and manifestations as in patients without MC. However, cardiovascular symptoms, such as dizziness, tachycardia, hypotension, and/or syncope, tend to be more common and skin reactions, such as urticaria and angioedema, respiratory symptoms, and gastrointestinal reactions less frequent.^{22,23} In comparison with patients with idiopathic anaphylaxis without MC, in patients with ISM, hypotension in the absence of urticaria occurred significantly more often.³³ The severity of anaphylaxis in adults with ISM seems to be increased. In one study, 48% of reactions were classified as severe and 38% resulted in unconsciousness²²; another study reported unconsciousness in 72% of patients.²³

TRIGGERS OF ANAPHYLAXIS IN MASTOCYTOSIS

Most frequently reported triggers for anaphylaxis in adults with MC are Hymenoptera stings, whereas food and medication are reported less frequently.²² In unselected patients with food or drug anaphylaxis, elevated basal serum tryptase levels and MC are uncommon.³⁴ Physical stimuli, such as exposition to heat or cold, fast changes of temperature, rubbing of skin lesions (Darier sign), or stress and anxiety can lead to mast cell activation.² Anaphylaxis after jumping into cold water has been reported anecdotally. If no potential trigger is found, idiopathic anaphylaxis is diagnosed.³⁵

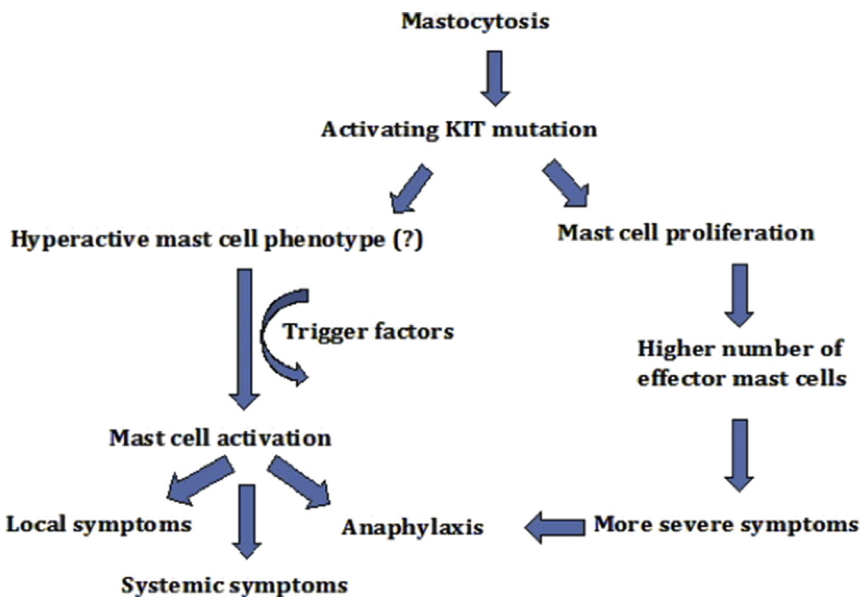


Fig. 1. Model for pathogenesis of anaphylaxis in mastocytosis.

Hymenoptera Venom Anaphylaxis in Mastocytosis

Elevated baseline tryptase levels or urticaria pigmentosa have been found in about 5% to 15% of those patients with Hymenoptera venom anaphylaxis (HVA),^{36,37} both indicating a possible underlying mast cell disease, such as SM. Most patients with SM without MIS are diagnosed in the follow-up of Hymenoptera venom allergy and elevated tryptase levels. MC has been identified to be a risk factor for severe anaphylaxis to Hymenoptera venom³⁷ and in patients with honey bee or vespid venom allergy, elevated baseline serum tryptase values were associated with the risk of severe anaphylaxis.³⁸

Having an increased risk of severe reactions, the correct diagnosis and therapy for HVA is important for patients with SM. Unfortunately, in MC total sIgE levels are often lower, which leads more often to negative sIgE and negative skin tests compared with patients with HVA without MC.³⁹ Thus, it might be necessary to use recombinant allergens (Ves v1/5 and Api m1-4/10) and a diagnostic cutoff of 0.1 KU/L in patients with low total sIgE to diagnose HVA correctly.⁴⁰ An additional diagnostic tool to use in these patients is the basophil activation test, which is sometimes able to confirm sensitization or to identify the culprit insect.⁴¹

Idiopathic Anaphylaxis in Mastocytosis

Idiopathic anaphylaxis is common in patients with MC.²³ No trigger factors are found in about 67% of all anaphylactic reactions in children and in 13% of the adult cases.²² Before idiopathic anaphylaxis is diagnosed, all potential triggers have to be ruled out.

Food Anaphylaxis in Mastocytosis

Whereas many adult patients with MC suspect foods as triggers of anaphylaxis, in only few of them can these triggers be confirmed.^{19,22,23} Nevertheless, recently published cases indicate that food allergy has to be considered in patients with MC. One patient with ISM presented with greater than 10 anaphylactic episodes after eating meat. In this patient, the provocation test with pork resulted in delayed occurring severe anaphylaxis despite low levels of specific IgE to meats and galactose- α -1,3-galactose.⁴² Two other cases of IgE-mediated fish- and crustacean-induced anaphylaxis were reported, where further assessment showed an underlying ISM.⁴³

Anaphylaxis Caused by Drugs

Only a minority of cases with drug-induced anaphylaxis are associated with MC. Many of them were related to general anesthesia, others to nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, contrast media, β -lactams, or other drugs typically leading to anaphylaxis.⁴⁴ Anaphylaxis during general anesthesia is an area of concern.^{45,46} In patients with MC who underwent different kinds of anesthetic techniques (general, local, and epidural anesthesia or sedation) 2% of the adult cases and 4% of the pediatric cases have been reported to develop perioperative symptoms related to mast cell activation, resulting in anaphylaxis in 0.4% of the adults and in 1 out of 40 children.⁴⁷ Symptoms presenting in adults were hypotension, cardiorespiratory arrest, coagulopathy, generalized urticaria, and loss of consciousness, whereas bronchospasm and generalized erythema was present in the pediatric case. Severe anaphylaxis has anecdotally been reported in patients with SM after intake of acetylsalicylic acid.⁴⁸

However, MC was an uncommon diagnosis when patients with hypersensitivity reactions to NSAIDs were analyzed. In patients with NSAID hypersensitivity, no

association to elevated basal serum tryptase levels was found, which is in contrast to patients with HVA.⁴⁹

Anaphylaxis in the Context of Mast Cell Activation Syndrome

For some patients and clinicians the term “mast cell activation syndrome” (MCAS) may be confusing. It has been introduced to propose a global unifying classification of all mast cell disorders.⁵⁰ The classification includes three distinct types of MCAS. (1) MC and MMCAS constitute primary MCAS. Patients with MMCAS have the same triggers for anaphylaxis as patients with MC (described previously).^{13,14,36} (2) Type I allergies are the main cause for secondary MCAS. (3) Idiopathic MCAS is the diagnosis, when no primary MCAS or trigger for secondary MCAS is found despite confirmed episodes with mast cell activation. Typical examples are idiopathic anaphylaxis or chronic sporadic urticaria. Thus, if a patient had MC, HVA anaphylaxis, and idiopathic anaphylaxis together, he or she would fulfill criteria for primary, secondary, and idiopathic MCAS. However, there is no additional benefit in calling anaphylaxis secondary (allergic) or idiopathic MCAS, because it is a well-recognized and well-described entity itself. Patients believing to suffer from idiopathic MCAS with polysymptomatic symptoms compatible with mast cell activation (eg, chronic diarrhea, headache, pruritus) do not seem to have an obviously increased risk for anaphylaxis.

ACUTE MANAGEMENT

Because patients with MC have a high risk for anaphylactic reactions and often present more severe symptoms than patients without MC, immediate therapy is necessary and delay may result in fatal reactions.⁵¹ The first-line medication is epinephrine, administered at a dose of 0.3 mg to 0.5 mg in adults and 0.01 mg/kg in children. This should be primarily administered intramuscularly and can be repeated every 5 to 15 minutes, if necessary.^{11,52} In cases of severe hypotension or cardiac arrest an intravenous bolus infusion under monitoring cardiac response is suggested (eg, 1–10 µg/min). Supporting measures are high-flow oxygen, positioning the patient in the flat Trendelenburg position, and volume replacement.

Bronchospasm responds best to inhaled β-agonists (eg, salbutamol) or epinephrine. Other therapeutics are H₁ and H₂ antihistamines. Steroids are often given; however, their action seems to be on the prevention of protracted or biphasic reactions than in the acute management of anaphylactic reactions because of their slow onset of action.¹¹

CHRONIC MANAGEMENT

Emergency Preparedness

Adults with MC and children with extensive skin involvement or high levels of serum tryptase have a high risk of anaphylaxis. For these patients it is recommended to carry an epinephrine autoinjector at all times.⁵³ In German-speaking countries, emergency kits also contain a rapid-acting H₁ antihistamine (eg, dimethindene or cetirizine) and a corticosteroid (eg, betamethasone), both for oral use.⁵⁴ When handing out an emergency kit, it is important to provide an appropriate instruction how to use the emergency medication, or even better an anaphylaxis education.⁵⁵ It should be ensured that the patient and his or her close environment recognize anaphylaxis, can use the epinephrine autoinjector correctly, and are instructed to call for professional help immediately.⁵⁶ In Germany an MC pass is handed out to the patient with information on acute treatment, prescribed emergency medication, and drugs to avoid or to be given under medical supervision.

Venom Immunotherapy in Mastocytosis

Venom immunotherapy (VIT) is recommended for all patients with Hymenoptera allergy (general urticaria, angioedema, or anaphylaxis) and MC. In patients with MC side effects are more frequent than in general patients with HVA, especially in those with yellow jacket venom allergy.⁵⁷ Systemic reactions to VIT seem to happen in 18%⁵⁸ to 24%⁵⁹ of treated patients with SM, whereas VIT was generally tolerated without any side effects in patients with CM.⁶⁰ Moreover, in MC the efficacy of VIT is slightly reduced, indicated by higher rates of systemic reactions to sting challenges during the first year of VIT.⁵⁸ Most of those patients are protected by an increase of the maintenance dose to 150 µg or 200 µg.⁶¹ In patients with SM who discontinued VIT after uneventful treatment, cases of fatal anaphylactic reactions have been described after being restung by the culprit insect. This has been described for yellow jacket and honey bee venom allergy.^{62,63}

In summary, VIT is highly recommended for patients with Hymenoptera allergy and SM. It should be optimally performed either with a sting challenge to control efficacy or with an increased maintenance dose of 200 µg and should best be carried out lifelong.

Anesthesia in Patients with Mastocytosis

MC is not a contraindication for anesthesia. Most patients with anaphylaxis after anesthesia had previously unrecognized SM. If this diagnosis is known, precautions may be taken and emergency preparedness may be achieved. It has been recommended to administer a prophylactic premedication before anesthesia. Most premedications include an H₁ (and possibly an H₂ antihistamine) and/or corticosteroids. However, the efficacy of such a premedication in this setting has not been proven. In one study in children with severe CM where no specific premedication had been given, but where the anesthesiologists chose the appropriate conditions, no serious adverse event occurred out of 29 diagnostic and surgical procedures.⁶⁴ Thus, deviations from routine anesthesia techniques are not necessarily warranted. However, a meticulous preparation and understanding of anesthetic implications are advised. For example, it may be considered to reduce stress and anxiety by the use of benzodiazepines and to avoid temperature changes and mechanical stimulation for the patient.^{2,47}

Further Treatment Options for Severe Cases of Recurrent Anaphylaxis

Recent publications show that omalizumab has proven to prevent symptoms, such as urticaria, gastrointestinal affliction, and hypotension, and can help to reduce adverse events during VIT.⁶⁵ This therapy has also shown to be effective in patients with idiopathic anaphylaxis and MC. The first approach, however, may be to administer high doses of antimediator therapy (H₁ and H₂ antihistamines, cromoglycate, montelukast), which is often sufficient (authors' personal experience).

In patients with recurrent severe life-threatening anaphylactic episodes caused by mast cell activation and a huge mast cell burden, cytoreductive therapy has been considered. It was shown that the frequency of such episodes was decreased after cladribine (2CdA) therapy.⁶⁶ Another therapy is tyrosine kinase inhibitors targeting the mast cell growth receptor KIT. A recently published study showed efficacy of the multikinase inhibitor midostaurin in patients with advanced SM, being able to reduce organ damage and disease progression.⁶⁷ However, data are not yet sufficient to recommend such an approach for anaphylaxis treatment. Another future therapy option may be the development of blocking antibodies directed against cell surface antigens expressed on mast cells, such as CD25, CD30, CD33, or CD52.⁶⁸

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