

The Problem of Anaphylaxis and Mastocytosis

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Mastocytosis is a rare disease characterized by an elevated whole body mast cell number. Anaphylaxis is a severe, generalized hypersensitivity reaction with rapid onset. The problem of anaphylaxis and mastocytosis is due to strongly increased mediator release from the elevated mast cell number during allergic reactions. This explains the much higher prevalence of anaphylaxis in mastocytosis than in the general population and its severe and sometimes fatal course. Because of the increased risk of anaphylaxis in mastocytosis, all patients with severe or recurrent anaphylaxis should be analyzed for underlying mastocytosis by estimation of baseline serum tryptase. If this is elevated, patients also should be tested via skin examination for cutaneous mastocytosis and with a bone marrow biopsy. All patients with mastocytosis and anaphylaxis must be instructed about avoiding the responsible elicitors and should carry an emergency kit with adrenaline for self-application. In mastocytosis patients with anaphylaxis due to Hymenoptera stings, venom immunotherapy is recommended for life.

Introduction

Mastocytosis is a rare organic disease with cutaneous and systemic involvement and most often a benign long-term course. Anaphylaxis is an infrequent, severe, systemic hypersensitivity reaction that can be fatal. What are the problems regarding the association of these two conditions? We start with a case presentation.

Case presentation

A male patient born in 1953 developed two systemic anaphylactic reactions with severe dyspnea, collapse,

and unconsciousness after honeybee stings in 1967 and 1984, whereas vespid stings were always well tolerated [1]. Judging from history and skin tests, there was no atopic constitution. In the presence of high exposure to Hymenoptera stings (as a hobby gardener) and positive skin tests and specific serum IgE antibodies to bee venom, immunotherapy with bee venom was started in 1984 but caused repeated systemic allergic side effects. Finally, the maintenance dose of 100 µg was well tolerated under antihistamine premedication and passive immunotherapy with beekeeper gammaglobulin [2]. Venom immunotherapy (VIT) could be continued without premedication until 1988. During this treatment, three bee stings were well tolerated without systemic allergic symptoms. After stopping VIT, additional honeybee stings occurred until 1994 and caused no systemic allergic symptoms.

In 1984 and 1994, however, the patient developed anaphylactic symptoms after intake of nonsteroidal anti-rheumatic drugs (and, since 1985, after eating honey). In 1994, he was examined for repeated anaphylactic reactions during postprandial exercise; another allergist documented hypersensitivity to various other foods. In early-2003, his blood pressure dropped severely during general anesthesia. In July of the same year, he was stung by a *Vespula* sp while gardening, developed severe dyspnea, and collapsed, although the EpiPen (DEY, Napa, CA) (adrenaline, 0.3 mg intramuscularly) was applied immediately by his wife. The emergency team arrived rapidly, and the patient was resuscitated, intubated, and transported to the intensive care unit of a university hospital. Stable cardiovascular and respiratory states were reached under volume substitution and noradrenaline infusions. However, because of severe hypoxic brain damage, he died 9 days later without having regained consciousness. The serum tryptase at hospital entry was greater than 1000 µg/L (normal value < 11.4 µg/L), and the retrospective analysis of a serum obtained in 1988 revealed a baseline serum tryptase (bT) level of 87.7 µg/L. Autopsy confirmed the presence of systemic mastocytosis (SM) in the bone marrow (Fig. 1). Based on these findings, there is no doubt that the repeated anaphylactic episodes due to various different elicitors—venoms, drugs, food, and exercise—since 1967 and the fatal course of the final *Vespula* sp sting in 2003 were due in significant part to SM.

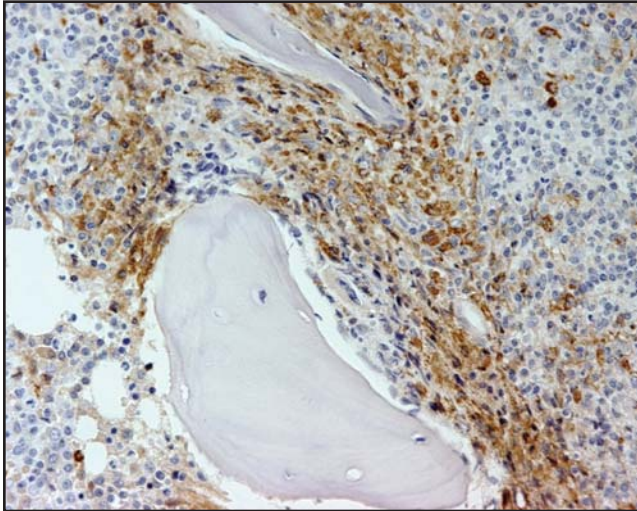


Figure 1. Bone marrow biopsy of a patient with fatal anaphylaxis after a *Vespa* spp sting showing extensive mast cell infiltrates (staining with marked antitryptase antibody).

In this article, we inform about actual definitions of anaphylaxis and mastocytosis, then summarize the published results of anaphylaxis in patients with mastocytosis, discuss the significance of an elevated bT without documented mastocytosis, and finally discuss the preventive and treatment measures in patients with SM and elevated bT.

What Is Anaphylaxis?

The World Allergy Organization defines anaphylaxis as a severe, life-threatening, generalized or systemic hypersensitivity reaction [3]. The Anaphylaxis Network Symposium of the United States [4] defines it as a serious allergic reaction that is rapid in onset and may cause death. The term *hypersensitivity* instead of *allergic reaction* is preferred by the World Allergy Organization because in some cases, no immunologic mechanism—IgE-, IgG-, and immune complex complement-related—can be detected. The major symptoms of anaphylaxis are caused by mediator release from mast cells (histamine, leukotriene C₄, prostaglandin D₂, tryptase, chymase, carboxypeptidase, and heparin). They are observed in the skin (urticaria, angioedema, flushing), mucosal tissue (swelling of the tongue, uvula, and intestinal mucosa resulting in dysphagia, abdominal cramps, vomiting, and diarrhea), respiratory tract (dyspnea, wheezing, stridor, reduced peak flow, and hypoxemia), and cardiovascular system (drop in blood pressure, syncope, and incontinence). According to recent US criteria, at minimum, respiratory compromise or arterial hypotonia should be present to justify the term *anaphylaxis* [4].

The major causes of anaphylaxis are foods (eg, peanuts, seafood, milk, and vegetables), drugs (eg, antibiotics, antirheumatics, general anesthetics, x-ray contrast media,

and others), and Hymenoptera venoms (honeybees and vespids). Whereas food anaphylaxis is usually associated with an atopic constitution, and respiratory tract involvement is dominant, drug- and venom-induced anaphylaxis is not more common in atopic than nonatopic individuals, and cardiovascular symptoms are more prevalent [5].

The incidence of anaphylaxis in large studies [6–8] varies between 8 and 30 cases per 100,000 inhabitants per year. The lifetime prevalence of severe anaphylaxis therefore may be approximately 1%. The annual fatality rate from anaphylaxis is estimated at about one fatality per 1 million inhabitants, indicating that about 1% of cases of severe anaphylaxis are fatal. The considerable variation in prevalence data may be due to different definitions of anaphylaxis or to environmental factors. Fatalities are probably underestimated [5–11].

What Is Mastocytosis?

Mastocytosis includes a large spectrum of disorders with widely differing clinical severity, from asymptomatic with normal life expectancy to highly aggressive [12•,13]. It is thought to be a rare disorder, with a prevalence of 1 case in 1000 to 8000 patients attending a dermatologic outpatient clinic. This may be an underestimation, because mastocytosis can present without cutaneous symptoms, and patients with mastocytosis are also seen by hematologists, allergists, oncologists, and other specialists. Mastocytosis is associated with an elevation of mast cells, especially in the skin, bone marrow, gastrointestinal tract, liver, spleen, and lymph nodes. Symptoms do not always correlate with the number of mast cells in the body [14,15••].

Most of the clinical symptoms are due to liberation of mast cell mediators such as histamine, tryptase, chymase, carboxypeptidase, heparin, prostaglandin D₂, and leukotriene C₄. Symptoms frequently involve the skin (pruritus and flushing), gastrointestinal tract (nausea, abdominal pain/cramps, diarrhea, and dyspepsia/gastrointestinal ulcer), and cardiovascular system (dizziness, weakness, palpitation, and drop in blood pressure to the point of unconsciousness). Bone and soft tissue pain, as well as neuropsychiatric symptoms (headaches, cognitive problems, and paresthesia), also may arise.

The mediator release in mastocytosis can occur through a non-IgE-mediated mechanism and be triggered by physical stimuli (eg, temperature change, pressure, rubbing/Darier's sign, and exercise), certain medications (eg, opioid analgesics, anesthetic agents, x-ray contrast media, and aspirin/NSAIDs), and emotional stress [15••]. Anaphylactic reactions also may occur as a result of immunologic—mostly IgE-mediated—reactions that are discussed in more detail subsequently.

Besides the mediator-induced symptoms, certain clinical manifestations can also be due to mast cell infiltration leading to osteoporosis with pathologic fractures,

cytopenia, hepatosplenomegaly, malabsorption, lymphadenopathy, or other organ dysfunctions [16].

In 2001, diagnostic criteria for and classification of SM based on an international consensus conference were published [17]. To establish the formal diagnosis of SM, one major criterion and one minor criterion, or three minor criteria, are required. The major criterion is defined as mast cell infiltrates in aggregates of greater than 15 found in a tissue other than skin (typically bone marrow). Minor criteria are an elevated bT ($> 20 \mu\text{g/L}$), abnormal mast cell morphology (spindle-shaped appearance, abnormal granulation, or cytoplasmic projections), surface staining of mast cells for CD2 and CD25, and detection of a codon 816 *c-kit* mutation in lesional tissue. In most adult patients with SM (~90%) and some with cutaneous mastocytosis (CM), an activation mutation in the *c-kit* gene, usually a point mutation on codon 816 (exon 17), is the genetic basis of the disease [14].

Classification of mastocytosis

The World Health Organization classification defines seven mastocytosis variants according to clinical and pathologic findings: CM, indolent SM (ISM), SM with an associated clonal hematologic non-mast cell lineage disease (SM-AHNMD), aggressive SM (ASM), mast cell leukemia (MCL), mast cell sarcoma (MCS), and extracutaneous mastocytoma [12•].

CM is characterized by the presence of skin lesions (most commonly urticaria pigmentosa, less frequently telangiectasia macularis eruptiva perstans, diffuse CM, and—mostly in children—cutaneous mastocytoma) without bone marrow or other internal organ infiltration by mast cells [18]. CM is the most common form in children and has a good prognosis, with regression or improvement of lesions in most by adolescence [19]. However, adult-onset urticaria pigmentosa is usually associated with SM [15•,20]. ISM is the most frequent presentation of mastocytosis in adults. A skin involvement usually is present, but up to 20% of patients (mainly adults) are diagnosed with mastocytosis without skin lesions [15••]. The course is mostly persistent or slowly progressive, the clinical symptoms may be minimal or pronounced, and the prognosis is usually good [17]. The rare severe forms with a bad prognosis are due to associated hematologic disorders (SM-AHNMD), ASM, MCL, and MCS [17].

Allergy and Anaphylaxis in Patients With Mastocytosis

Symptoms of mediator release (eg, recurrent flushing, itching, headache, palpitations, abdominal pain and diarrhea, dyspnea, and drop in blood pressure) are often observed in patients with SM but are also typical for anaphylaxis due to IgE-mediated allergic reactions. In several studies, an atopic constitution in patients with mastocytosis was

not found more frequently than in the total population [21,22••,23••]. Total IgE in patients with urticaria pigmentosa was even found to be significantly lower than in the general population [21], which can be explained by increased absorption of circulating IgE to abundant mast cells. This finding was later confirmed in patients with ISM [22••,23••]. Anaphylaxis in patients with mastocytosis is expected to be especially severe due to strongly increased mediator release from the high whole body mast cell number, illustrated by the extremely high tryptase value ($> 1000 \mu\text{g/L}$) found in our case presentation.

Occasional severe or even fatal cases of anaphylaxis in patients with mastocytosis have been published for many years, and an IgE-mediated allergic reaction was documented in most of these cases. Hymenoptera venoms were the eliciting allergens in most of these reports [1,24–29]. Several fatal systemic reactions to Hymenoptera stings in patients with mastocytosis have been documented [1,28,29]. Case reports of severe or fatal anaphylaxis in patients with mastocytosis to other elicitors, such as foods, muscle relaxants, and other drugs [30–33], also have been published.

In three recent retrospective studies, many patients with mastocytosis—children and adults—have been analyzed with regard to a history of anaphylaxis (Table 1) [22••,23••,33]. In all three studies, cutaneous forms of mastocytosis—mostly urticaria pigmentosa—and ISM were by far the most common forms in adults and children, seen in 351 of 370 total patients (94.8%). More severe forms, such as SM-AHNMD ($n = 8$), ASM ($n = 10$), or MCL ($n = 1$), were found in only a small minority of patients. bT levels were elevated above $11.4 \mu\text{g/L}$ in more than 90% of patients ($> 20 \mu\text{g/L}$ in most), especially in adults and patients with documented SM, but in all three studies, occasional normal values were found, even in patients with ISM and SM-AHNMD.

Anaphylaxis was reported in 20% to 49% of adults and in 6% to 9% of children with mastocytosis. This is definitely strongly increased compared with the general population. In two studies, a considerable number of patients reported repeated episodes of anaphylaxis, some more than three times per year [23••,33].

Anaphylaxis risk in children increased parallel to the extent and the density of CM. Anaphylaxis was significantly more common in adults with SM than in those with only cutaneous forms, especially in those with ISM without skin involvement. bT was significantly higher in patients with anaphylaxis compared with those without it [23••].

Anaphylaxis was most frequently caused by Hymenoptera stings, drugs, and foods in patients with and without mastocytosis. Other reported causes were latex, alcohol, exercise, and postural changes, often in combination with other elicitors [16]. No definitive cause could be found in 17% [23••] and 37% [22••] of patients in two studies.

According to one study, specific IgE to the causal agent can be found only in a minority of patients with

Table 1. Anaphylaxis in patients with mastocytosis as reported in three recent retrospective studies

	Florian et al. [33]	González de Olano et al. [22••]		Brockow et al. [23••]	
	Adults	Adults	Children	Adults	Children
Patients with mastocytosis, <i>n</i>	40	163	47	74	46
Mastocytosis classification					
Cutaneous only, <i>n</i> (%)	0	8 (5)	47*	13 (18)	46*
ISM, <i>n</i> (%)	29 (73)	149 (86)		59 (80)	
SM-AHNMD, ASM, MCL, <i>n</i> (%)	11 (37)	6 (4)		2 (2)	
Serum tryptase level					
% > 11.4 µg/L	97	ND		ND	
% > 20.0 µg/L	87	ND		ND	
Median, µg/L	ND	26.7		25.5	6
Range, µg/L	ND	4–550	3–115	3–200	1–46
Atopy, <i>n</i> (%)	ND	39 (24)	8 (17)	21 (28)	5 (11)
Patients with anaphylaxis, <i>n</i> (%)	8 (20)	36 (22)	3 (6)	36 (49)	4 (9)
Episodes	ND	ND	ND	57	10
Due to drugs	ND	9	0	13	1
Due to food	ND	3	1	18	2
Due to insect stings	Mostly	9	0	20	0
Due to other causes	ND	15	2	6	1

*Bone marrow biopsy not done in children.

ASM—aggressive systemic mastocytosis; ISM—indolent systemic mastocytosis; MCL—mast cell leukemia; ND—no data available; SM-AHNMD—systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease.

anaphylaxis [22••]. However, in patients with mastocytosis and anaphylaxis to Hymenoptera stings, sensitivity to the respective venom was detected by routine diagnostic tests—intracutaneous skin tests and/or venom-specific IgE—in 8 of 10 patients in one study [27] and in 52 of 55 in a more recent publication [34••].

According to several publications [1,26,32], mastocytosis was sometimes detected only after one or more episodes of severe anaphylaxis or at autopsy. Therefore, clinicians are strongly recommended to look for mastocytosis in all cases of recurrent and severe anaphylaxis and, if possible, to perform autopsies in cases of fatal anaphylaxis.

Elevated Baseline Tryptase in Patients With Hymenoptera Venom Allergy

Tryptase is a serine protease and the most important marker of the whole body mast cell load. The commercially available fluorescence immunoassay measures total tryptase. Both α - and pro- β -tryptase are secreted continuously. β -tryptase is stored in mast cell granula and released during mast cell activation. It is a marker of anaphylaxis and should be measured within 1 to 5 hours after symptom onset (in comparison with bT, which is estimated before or at least 1 week after an assumed anaphylactic reaction) [35,36]. Elevated bT

levels are seen in CM and SM. Values greater than 20 µg/L strongly suggest systemic involvement, and further investigations, including bone marrow biopsy, are recommended. For bT values below 20 µg/L, the diagnostic approach is guided by the history and the clinic. However, normal levels of bT do not exclude the presence of mastocytosis [17].

In sting challenge studies in Hymenoptera venom-allergic patients, those who developed severe anaphylaxis showed not only a strong increase in serum tryptase during the reaction but also had on average a higher bT when compared with those who did not react or who developed only mild allergic symptoms [36]. Two subsequent studies of large numbers of patients with a history of systemic allergic reactions to insect stings confirmed these results [37,38]. They also showed an incidence of elevated bT in 15% to 25% of patients with a history of severe anaphylaxis after Hymenoptera stings, compared with only about 5% in those with mild allergic reactions.

Because of the association of bT above 11.4 µg/L with a risk of especially severe, sometimes IgE-negative, systemic Hymenoptera sting reactions and also with CM, ISM, or other forms of mastocytosis, this enzyme should be determined in all patients with a history of systemic allergic sting reactions [37–39].

Table 2. Safety and efficacy of venom immunotherapy in 47 adult patients with mastocytosis

	Fricker et al. [27]	González de Olano et al. [44••]	Bonadonna et al. [45•]
Patients on VIT, <i>n</i>	10	21	16
Mastocytosis classification	Urticaria pigmentosa	Indolent systemic mastocytosis	Indolent systemic mastocytosis
Grade of anaphylaxis			
Respiratory	0	1	0
Cardiovascular	10	20	16
Insect			
Honeybee	4	6	1
<i>Vespula</i> spp	6	7	8
<i>Polistes</i> spp	0	8	7
Intracutaneous skin tests positive ≤ 0.1 $\mu\text{g/mL}$	8	18	Not reported
Venom-specific IgE ≥ 0.35 kU/L	5 (Phadebas test)	20 (CAP)	Not reported
Patients with allergic side effects, <i>n</i>	2	6	2
Cutaneous, <i>n</i>	2	1	2
Cardiovascular, <i>n</i>	0	5	0
Patients re-exposed during VIT, <i>n</i>	8	12	13
Reaction			
Only local, <i>n</i>	7	9	11
Cutaneous, <i>n</i>	1	1	0
Respiratory, <i>n</i>	0	1	0
Cardiovascular, <i>n</i>	0	1	2

VIT—venom immunotherapy.

Preventive and Treatment Measures in Patients With Mastocytosis and Anaphylaxis

This review does not aim to offer an extensive description of treatment of mastocytosis. We instead concentrate on managing symptoms of increased mediator release due to a nonimmunologic or an immunologic—mostly IgE-mediated—mechanism. With regard to treatment for symptoms of mastocytosis due to organ infiltration with mast cells (eg, osteoporosis) and for SM-AHNMD, ASM, and MCL, we refer to recent extensive reviews [12•,40,41••]. For treatment of episodes of acute anaphylaxis, the recommendations are the same as for anaphylaxis without mastocytosis [4,42]. Management includes recumbent position; intramuscular injection of adrenaline; volume substitution; intravenous injection of H1 antihistamines and corticosteroids; inhalation of β_2 -stimulating drugs; and, if necessary, resuscitation measures.

Many patients with mastocytosis report minor episodes of symptoms of mediator release—like flushing, itching, dizziness, and abdominal cramps after physical factors (heat, cold, pressure, rubbing, exercise) or alcohol or drug intake. In patients with recurrent episodes, continuous prophylactic medication with nonsedating H1

antihistamines is recommended. If insufficient, an H2 antihistamine and eventually an antileukotriene can be added [40]. In patients with abdominal symptoms, oral sodium cromoglycate may be helpful [43].

All mastocytosis patients with definitive anaphylaxis should receive an emergency kit [34••] that includes adrenaline for self-application (EpiPen), as well as tablets of a rapidly acting H1 antihistamine (eg, l-cetirizine, two tablets of 5 mg) and a corticosteroid (prednisolone, two tablets of 50 mg). Oral and written instructions about using the kit and avoiding re-exposure with the eliciting agent must be given. In drug-induced anaphylaxis, alternative drugs should be recommended and tested under clinical conditions. A special risk situation is general anesthesia. Anesthetists must be informed about the mastocytosis before the intervention and should avoid using mediator releasers such as opiates, muscle relaxants, and x-ray contrast media if possible.

In Hymenoptera sting-induced anaphylaxis, VIT is indicated. Three studies showed that this treatment is well tolerated by most patients with mastocytosis and also protects most from further anaphylactic sting reactions (Table 2) [27,44••,45•]. The first study dates back to the

mid-1990s [27]. All 10 adult patients had histologically confirmed urticaria pigmentosa, and 3 also had a bone marrow biopsy indicating ISM. That only 50% of patients had venom-specific IgE in this study compared with the second study [44••] may be explained by the use of the then-available Phadebas test (Phadia, Uppsala, Sweden), which was much less sensitive than the CAP (Phadia, Uppsala, Sweden), which is most often used today. In the second and third studies, all patients were classified as ISM [44••,45•]. Although most patients tolerate VIT without problems, individual patients may develop severe and recurrent side effects from VIT that make it difficult to reach the typically recommended maintenance dose of 100 µg [1,44••,46]. Therefore, we recommend premedication with an H1 antihistamine during the dose-increase phase of VIT [47]. A recent report described successful prophylactic treatment with omalizumab, the humanized monoclonal mouse antibody to Fcε, in such a patient that allowed the patient to reach the maintenance dose without experiencing further side effects [46]. Because three fatal sting reactions in mastocytosis patients have been described after stopping VIT thus far [1,28], it is generally recommended to continue VIT for life in patients with mastocytosis and venom-induced anaphylaxis [34••,48]. Although most patients with mastocytosis are protected by VIT, a minority may develop systemic allergic symptoms after a re-exposure [27,44••,45•]. In this situation, it is recommended to increase the maintenance dose to 200 µg [34••].

As venom-allergic patients with elevated bT but no proven mastocytosis are also at an increased risk of developing very severe anaphylaxis, it is recommended to continue VIT for life in this group as well [37,38]. In 161 venom-allergic patients (104 to bee venom, 57 to *Vespula* spp venom), the sting challenge during VIT induced a systemic, mostly mild allergic reaction, indicating an incomplete protection more often in patients with elevated than with normal bT. Still, most patients (60%) with elevated bT were fully protected. The difference between patients with and without elevated bT was somewhat higher for *Vespula* spp venom-allergic patients [38].

In patients with mastocytosis and those with elevated bT without proven mastocytosis and a history of anaphylactic reactions to Hymenoptera stings, we recommend carrying an emergency medication set for life.

Conclusions

Patients with SM, especially adults, are at a highly increased risk to develop severe or even fatal anaphylaxis, most often due to allergens such as Hymenoptera venoms, drugs, and foods. A history of severe and/or repeated anaphylaxis indicates the possibility of underlying SM. Determination of bT, dermatologic examination of the skin for CM, and bone marrow biopsy are further steps to diagnose or exclude the presence of mastocytosis. Patients

with mastocytosis and anaphylaxis should undergo careful allergologic examination for identification of responsible allergens. They must obtain oral and written instructions about avoidance measures and should carry an emergency kit that includes adrenaline for self-application. In patients with anaphylaxis due to Hymenoptera stings and mastocytosis, VIT has been shown to be effective and is recommended for life.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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