

Stinging Hymenoptera and mastocytosis

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Purpose of review

Patients suffering from mastocytosis are at risk for a particularly severe Hymenoptera sting anaphylaxis. The purpose of this review is to evaluate the current knowledge on pathophysiologic events, which might explain the specific risk of patients with mastocytosis.

Recent findings

Mast cell products can neutralize major toxins of snake or bee venoms. β -tryptase from mast cells is able to degrade allergens and IgE antibodies. Thus, mast cells and their mediators should protect patients from venom toxicity and should also lead to a decreased allergenicity. However, these theoretically beneficial effects of mast cells on downregulating allergic immediate type reactions are insufficient to protect patients with mastocytosis from severe anaphylaxis. In contrast, these patients are at an even higher risk. Many compounds of Hymenoptera venom can induce Fc ϵ receptor-independent mast cell degranulation. In the context of mast cell activation induced by Hymenoptera venom, Fc ϵ RI-dependent stimulation of mast cells via bridging of specific IgE-antibodies may be of particular importance. Abundance and dysfunction of mast cells in patients with mastocytosis may explain a significant portion of the particularly high anaphylactic risk in patients with mastocytosis.

Summary

The particular anaphylactic risk of patients with mastocytosis results from a variety of mechanisms. However, their individual contribution still needs further clarification.

Keywords

anaphylaxis, Hymenoptera venom allergy, mast cell, mastocytosis, serum tryptase

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Introduction

The present work is an extension of our recent review, which addressed possible clinical associations between mastocytosis and Hymenoptera venom allergy (HVA), and which was also published in this journal 3 years ago [1]. In that preceding review, we presented evidence that patients with mastocytosis are not only at an increased risk for HVA, but also for particularly severe sting anaphylaxis. Patients with mastocytosis, who suffer from HVA, develop life-threatening sting reactions after a field sting at a much greater frequency than do matched individuals who are also allergic to Hymenoptera venom, but who do not have mastocytosis. In mastocytosis patients, fatal sting reactions may already occur at the first anaphylactic reaction [2]. Venom immunotherapy (VIT) in patients with mastocytosis is associated with a significantly higher rate of severe side effects, which may even force treating physicians to stop VIT in individual patients [3]. However, it is possible today to achieve treatment tolerance in the majority of patients even if they have already sustained one or more anaphylactic reactions during VIT. Various treatment options are

available to reduce the risk for severe, VIT-associated side effects in mastocytosis patients [4]. Although VIT is effective in the latter patients, it may be necessary to use an elevated maintenance dose to protect individual patients [5].

Pathophysiologic mechanisms, which cause this specific anaphylactic risk in patients with mastocytosis and HVA, are still poorly described. It is well documented that, in addition to Hymenoptera venom, other immediate type allergens are fairly unimportant for eliciting severe anaphylactic reactions in mastocytosis patients. Several questions remain unanswered: why do these patients mainly react to Hymenoptera venom? Is the particularly high risk for severe anaphylaxis just due to the increased number of mast cells acting as effector cells of an immediate type allergy? Or might there also be a dysfunction of the mast cells to explain the increased risk for anaphylaxis?

In the current review we will try to present the most recent findings regarding the interactions between mastocytosis, mast cells, and Hymenoptera venom, and related anaphylactic reactions.

The putative protective role of mast cells: is resistance to venoms enhanced?

Recently, it was shown that mast cells can defend against envenomation. Endothelin-1 is an endogenous peptide with a potent vasoconstrictor activity being important during sepsis, asthma and atherosclerosis, and also during many other physiologic processes. A recent study [6] used an in-vivo model to evaluate the response of mice to intraperitoneally administered endothelin-1. In a first step, the authors presented evidence that endothelin-1 acts as a potent mast-cell activator leading to degranulation and mediator release. After endothelin injection, survival was comparable between mice with normal mast cell content, and mice which had originally been mast cell deficient, but which were reconstituted with mast cells before the experiment. On the contrary, all mast cell deficient animals developed severe diarrhoea, and approximately 70% died after endothelin exposure [6]. Later it was found that endothelin-1 has a high homology to sarafotoxin, the most potent toxic component of *Atractaspis engaddensis* (Israeli mole viper). The injection of sarafotoxin into the peritoneal cavity of mice induced a dose-dependent injury (reduction of body temperature, death) [7]. Mast cell deficient mice were much more susceptible to corresponding toxic effects than normal mice or reconstituted mice after mast-cell deficiency. Venom concentration measurements in the peritoneal fluid showed that normal mice had almost eliminated the toxin whereas toxin concentrations remained high in mice lacking mast cells [7]. These findings strongly suggest a protective role of mast cells for toxin elimination.

The key enzyme responsible for sarafotoxin elimination appears to be carboxypeptidase A, which is one of the proteases contained in mast cells. If healthy mice are exposed to snake venom in combination with an inhibitor of carboxypeptidase A, they are more susceptible to venom-related toxic effects and die within 1 h. Similar protective effects of mast cells have been described with regard to honeybee venom elimination. However, it is still unclear whether mast cell-mediated honeybee venom clearance is also mediated by carboxypeptidase A or by other proteases.

Thus, mast cells may release compounds, which neutralize the major toxins of snake or bee venoms. It should be noted that corresponding knowledge has only been obtained on the basis of animal experiments. However, even if mast cell biology of the mouse may be different from that of humans [8], it is likely that human mast cells will exhibit a similar protective antivenom effect. Controlled mast cell activation and degranulation are of central importance for the antivenom effect, and these alterations of mast cell function must be regarded as

beneficial in mammals by nature aiming for protection and not harm of the individual.

The importance of enzymatically active tryptase for degradation of allergens and IgE-antibodies

Several isoenzymes of tryptase have been identified. The two isoenzymes that are most abundantly expressed in and secreted by mast cells are α -tryptase and β -tryptase. Plasma concentration of the latter can be measured by a commercially available test system (ImmunoCAP Tryptase, Phadia, Uppsala, Sweden). Mature β -tryptase is stored in mast cell granules as an enzymatically active protease and is released only after mast cell stimulation. The tryptase, which can be found in serum without specific mast cell activation, consists of enzymatically inactive protryptases. These pro-tryptases are spontaneously secreted by resting mast cells [9]. The physiologic role of these inactive tryptases is unclear.

The release of mediators upon mast cell stimulation is also part of a negative feed back loop controlling mast cell activation. β -tryptase, which is released during acute mast cell degranulation, was shown to cleave aeroallergens into defined peptide fragments with a reduced allergenic activity [10]. Correspondingly, pharmacological protease inhibition will enhance mast cell degranulation. Furthermore, it was shown that β -tryptase cleaves specific-IgE to birch pollen allergen [11]. This cleavage abolishes the binding of IgE to the high-affinity mast cell Fc ϵ receptor and reduces reactions to allergens. These findings illustrate that mast cell proteases may possess a variety of downregulating effects reducing allergen-induced release of anaphylactic mast cell mediators such as histamine.

Thus, β -tryptase may degrade allergens and IgE antibodies. Therefore, the release of active β -tryptase during an allergic reaction should have a protective effect against venom toxicity and should also lead to a decreased allergenicity. However, this negative feed back loop seems not to be efficient enough to protect patients from severe anaphylaxis. The situation is even more complex in patients with mastocytosis where the increased mast cell burden does not decrease but actually increases the risk for anaphylaxis.

Hymenoptera venoms and mast cell activation

Mast cell activation can be caused by Fc ϵ receptor-dependent and Fc ϵ receptor-independent mechanisms. Hymenoptera venoms contain peptides and small molecules, which – except for mellitin – do not play a role as allergens. Some of these nonallergenic compounds may,

however, induce mast cell release via an IgE-independent mechanism. Several honeybee venom peptides have been identified which may cause degranulation of mast cells, for example, mellitin, melectin, and MCP peptide [12]. Vespid venom may also contain several such peptides, for example, mastoparan, bradykinin-related peptides, and Polybia-MPI, but also proteins with comparable action, for example phospholipase A [13–16]. Consequently, Hymenoptera venom can induce mast cell release by IgE-independent mechanisms. However, there is also evidence that related toxic effects of Hymenoptera venom are facultative and do not occur in all patients with mastocytosis. Many of these patients get stung periodically, but do not develop any allergic reaction.

In comparison to Fcε receptor-independent mechanisms, Fcε receptor-dependent pathways are significantly more important in the context of mast cell activation induced by Hymenoptera venom. Various venom proteins act as allergens and may induce the production of IgE-antibodies. Hymenoptera venom compounds act as strong sensitizers in the general population: venom-specific IgE antibodies are detected in about 25% of the healthy population [17]. Systemic allergic reactions to insect stings are reported by 0.3–7.5% of individuals in the United States and Europe [18,19]. In the vast majority of patients with sting anaphylaxis, venom sensitization can be demonstrated *in vitro* and/or by skin tests. Interestingly, compared with Hymenoptera venom allergic patients without mast cell disease, patients with mastocytosis show lower concentrations of venom-specific IgE (Rerink, Ruëff, unpublished data). Probably, venom-specific IgE is bound to Fcε-receptors on mast cells where it escapes measurement. However, if venom sensitization was defined as a positive skin test and/or a positive *in vitro* test, related sensitization rates did not differ significantly between patients who were suffering from mastocytosis and those who did not (Rerink, Ruëff, unpublished data).

In comparison to honeybee venom allergy, vespid venom allergy seems to be associated with a higher anaphylactic risk after a field sting: several fatal reactions have been reported in patients with mastocytosis after a vespid sting [2,20,21], and the majority of patients with mastocytosis

suffer from vespid venom allergy (Table 1) [22,23, 24*,25*].

It remains unclear why HVA is extraordinarily frequent in patients with mastocytosis. However, it should be noted that Hymenoptera venoms are also the most frequent elicitors of anaphylaxis among adult individuals of the general population [26–28]. Furthermore, vespid venom seems to be more dangerous during a field sting in unselected individuals than honeybee venom: large epidemiological studies found that severe, potentially life threatening field sting reactions were significantly more common in patients with vespid than with honeybee venom allergy [29,30]. Therefore, the peculiarities of HVA in patients with mastocytosis may simply be a reflection of immunologic phenomena important for the general population.

Increased mast cell number as an enhancing factor of anaphylaxis?

Mastocytosis is characterized by an increase of mast cell number in the skin and/or in internal organs (e.g. bone marrow, spleen, liver, lymph nodes, gut). Together with basophils, mast cells represent the most important effector cells of an acute immediate type reaction. It seems obvious that a variety of effector cells involved in anaphylaxis contribute to the risk for a very severe reaction.

It is assumed that baseline serum tryptase concentration reflects the mast cell burden of the body. Recently, it was found that almost 30% of the healthy population lacks the gene coding α-tryptase [31]. Later it was shown that the distribution of tryptase haplotype in patients with mastocytosis was consistent with the distribution in the general population [32]. Plasma tryptase levels in patients with mastocytosis were not affected by the pattern of α-tryptase or β-tryptase alleles, and total tryptase levels correlated positively with disease severity [32].

Compared with healthy individuals, baseline serum tryptase concentration is elevated in patients with mastocytosis. In these patients, increased tryptase concentrations are also associated with an increased risk for severe anaphylactic reactions. However, it remains unclear whether it is the total mast cell load represented by

Table 1 Vespid and/or honeybee venom allergy in adult patients with mastocytosis

First author	n	Type of patients	Bee venom allergy (%) ^a	Vespid venom allergy (%) ^b
Fricker <i>et al.</i> [22]	10	CM (70%), SM (30%)	40	60
Ludolph-Hauser <i>et al.</i> [23]	9	CM	10	90
Bonadonna <i>et al.</i> [24*]	16	SM	6	94
Brockow <i>et al.</i> [25*]	20	CM, SM	20	80
Ruëff, unpublished data	64	CM (33%), SM (67%)	33	84

CM, cutaneous mastocytosis; SM, systemic mastocytosis.

^aPercentage rates rounded. In parts patients were treated with both venoms.

baseline tryptase concentration or the type of mastocytosis or any mast cell disease, which increases the anaphylactic risk. Three arguments confound the issue:

- (1) A baseline serum tryptase concentration of more than 20 µg/l is one of four minor diagnostic criteria for systemic mastocytosis [33]. In patients with cutaneous mastocytosis, baseline serum tryptase may or may not be elevated, and also in patients with systemic mastocytosis, serum tryptase level does not always have to be increased.
- (2) Among our own mastocytosis patients with previous insect sting anaphylaxis, we identified 64 individuals in whom we had complete information on the type of mastocytosis by skin examination, bone marrow biopsy, and baseline serum tryptase. Twenty-one patients had a cutaneous mastocytosis and 43 fulfilled the diagnostic criteria for systemic mastocytosis. Two of the patients with systemic mastocytosis had a bone marrow mastocytosis without cutaneous manifestation, one patient had an associated hematologic disease. Moderate anaphylactic reactions were reported by 11, severe reactions (anaphylactic shock, loss of consciousness) by 42, and near fatal reactions by 11 patients. No significant association between the severity grade of the preceding sting reaction and the type of mastocytosis could be found.
- (3) Recently, systemic mastocytosis was diagnosed in 21 of 379 consecutive individuals (5.5%) with a history of insect sting anaphylaxis. Another nine patients (2.4%) did not allow the authors to diagnose mastocytosis according to standard definitions. These patients showed at least one (excluding raised serum tryptase concentration) or two minor diagnostic criteria characteristic of systemic mastocytosis [34^{*}]. Six of these nine patients also had a severe anaphylaxis and in eight patients, vespid venom allergy was diagnosed.

It is likely that an increased number of effector cells participating in anaphylactic reactions contribute to the particular risk of HVA. However, the interactions are complex. Patients with cutaneous mastocytosis are suffering from a minor disease and show a lower total body content of mast cells than patients with systemic mastocytosis. Furthermore, there are patients who do not suffer from mastocytosis according to the current diagnostic criteria, but who have another type of mast cell disease. Nevertheless, the severity of anaphylactic reactions is comparable. Therefore, they cannot be necessarily attributed to the total number of mast cells in the body, but must also involve functional alterations. This lack of association also means that the severity grade of a sting reaction must involve other risk factors such as older age, male sex, or ACE-inhibitor medication.

Is there a mast cell dysfunction in patients with mastocytosis?

Mutation of the activating receptor KIT is the key event involved in the pathogenesis of mastocytosis. This mutation leads to receptor activation without presence of a ligand (stem cell factor). Receptor activation then causes proliferation and enhanced survival of mast cells. KIT receptor activation may also modify histamine release by mast cells [35].

Another abnormal feature of systemic mastocytosis is the expression of certain adhesion molecules (CD2, CD25) on the mast cell surface, which are absent in mast cells from healthy individuals [36,37].

Furthermore, an overexpression of several adhesion-related and activation-related antigens such as CD63 [38], CD69 [39], and CD203c [40] was shown on mast cells from patients with indolent systemic mastocytosis. Surface membrane receptors involved in the binding of complement components and complement-mediated cell activation are also overexpressed in patients with systemic mastocytosis [41]. The number of cells expressing CD11, CD35 and CD88, and also the density of these receptors per cell were elevated significantly in patients with systemic mastocytosis. The CD88 receptor binds C5a, which may induce histamine release from synovial mast cells isolated from patients with rheumatoid arthritis [42].

Mast cell CD203c is upregulated in response to IgE receptor cross-linking [40], and overexpression of these receptors might contribute to the extraordinarily high risk for anaphylaxis in patients with mastocytosis.

It is highly likely that systemic mastocytosis is associated with a variety of immunophenotypic particularities, which may also increase the risk for severe anaphylactic events in these patients. However, it should be noted that most of the knowledge on these receptors and adhesion molecules and on their action stems from malignant human mast cell lines. It is unclear whether these findings can be translated into benign mast cells from patients with mastocytosis. Little is also known about alterations of mast cell function in patients with cutaneous mastocytosis. Therefore, much more work will be necessary to clarify the exact significance of functional alterations in mast cells responsible for cutaneous or systemic mastocytosis.

Conclusion

Hymenoptera venoms are potent allergens and Hymenoptera stings are major elicitors of anaphylactic reactions in the general population. A specific genetic disposition

such as atopy is not required for the onset of HVA. In patients who suffer from mastocytosis and a simultaneous HVA, several cofactors may aggravate the risk for a severe anaphylactic reaction after venom exposure: potential cofactors include the abundance and dysfunction of mast cells, and additional toxic venom effects, which are specific for mastocytosis. However, clarification of the precise pathophysiology remains a challenging open question.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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