

Hymenoptera Anaphylaxis as a Clonal Mast Cell Disorder



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KEYWORDS

- Systemic mastocytosis • Monoclonal mast cell activation syndrome
- Hymenoptera venom allergy • Anaphylaxis • Trypsase • Clonal mast cell disease

KEY POINTS

- Up to 7% of adult patients with Hymenoptera venom allergy may simultaneously suffer from a clonal mast cell disease.
- Patients with clonal mast cell disease and Hymenoptera venom anaphylaxis are commonly males, without skin lesions, and anaphylaxis is characterized by hypotension and syncope in the absence of urticaria and angioedema.
- A normal value of trypsase (≤ 11.4 ng/mL) in these patients does not exclude a mastocytosis.
- The diagnosis of a mast cell disease leads to several therapeutic consequences concerning the treatment of Hymenoptera venom allergy.
- These patients have to undergo long-life venom immunotherapy to prevent further, potentially fatal severe reactions.

INTRODUCTION

Mastocytosis is a clonal mast cell disorder (CMD) that encompasses a heterogeneous group of clonal disorders characterized by the proliferation and accumulation of mast cells (MC) in different tissues, with a preferential localization in the bone marrow (BM) and skin.¹ Subjects with mastocytosis can experience symptoms owing to a massive MC activation and release of mediators.

Systemic symptoms may include hypotension and anaphylactic shock, flushing, headache, itching, abdominal pain, dyspepsia, diarrhea, and bone and soft tissue pain.²

CMD includes cases not fulfilling sufficient criteria for systemic mastocytosis (SM) but showing MC clonality markers by expression CD25/CD2 on immunophenotyping

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and/or a KIT mutation at codon 816 on molecular analysis. These latter patients may have a limited, prediagnostic form of SM, also indicated as monoclonal MC activation syndrome (MMAS), but their risk of developing severe life-threatening anaphylaxis is similar to patients with SM.²⁻⁴

The prevalence of anaphylaxis in patients with mastocytosis is much higher than the 0.05% to 2.00% estimated frequency of anaphylaxis in the general population^{5,6} and has been reported to be between 22% and 49% in adults⁷⁻⁹ and between 6% and 9% in children^{7,8}; discrepancies between different studies might be a result of the heterogeneity of patient cohorts, the definition of anaphylaxis, and the sensitivity of diagnostic techniques.

A wide variety of stimuli (venom, drug, or food) can trigger anaphylaxis in patients with mastocytosis, but for certain patients no eliciting factors can be identified despite a comprehensive allergy workup and, therefore, we use the term idiopathic anaphylaxis. All epidemiologic studies have shown that Hymenoptera stings represent the most common trigger of anaphylaxis in subjects with mastocytosis.⁷⁻¹⁰

Hymenoptera Venom Allergy

Hymenoptera venom allergy (HVA) is a typical immunoglobulin (Ig)E-mediated disease, whose clinical manifestations are the result of the MC degranulation, which is triggered by the binding of the venom allergens to specific IgE (sIgE). Severity can vary from large local reactions to systemic anaphylaxis. The reactions are classified according to Mueller's scale with 4° of increasing severity.¹¹ Diagnostic procedures include skin prick and intradermal tests and serum-sIgE essays.

The insects responsible for allergic reactions are Hymenoptera belonging to the suborder Aculeate, which includes the Apidae, Vespidae, and Formicidae families (Fig. 1). The Apidae family includes *Apis mellifera* and *bombus*. The Vespidae family takes in the Vespinae subfamilies (*Vespula* species and *Vespa crabro*) and Polistinae subfamilies (*Polistes* species), among which *Polistes dominulus* is widespread especially in the Mediterranean area.¹² There is no preventive pharmacologic treatment

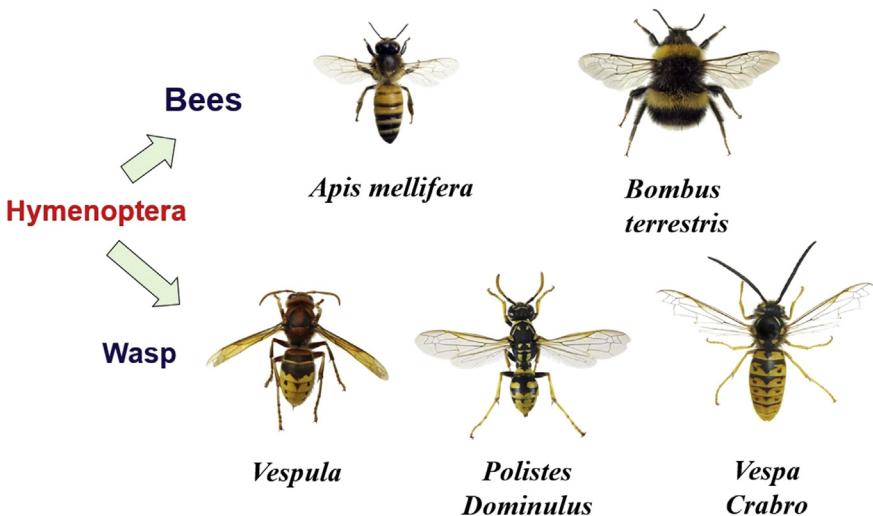


Fig. 1. Hymenoptera venom allergy and clonal mast cell disorders (CMD). (Courtesy of Analgero, Scarperia e San Piero FI, Italy.)

available for HVA. These patients should carry a self-administration emergency kit that includes oral antihistamines and corticosteroids as well as self-injectable epinephrine. Venom immunotherapy (VIT) represents a safe and effective treatment that decreases the risk of subsequent systemic reactions and reduces morbidity and mortality.¹³ VIT is prescribed to all subjects with a clear history of systemic reaction and positive skin test or venom sIgE in serum.

Hymenoptera Venom Allergy and Clonal Mast Cell Disease

During the last few years it has increasingly been realized that there is a preferential association between HVA and mastocytosis. First, the most common trigger of anaphylaxis in patients with mastocytosis is Hymenoptera venom. In 3 large case series that evaluated the causes of anaphylaxis in patients with mastocytosis, HVA was reported to range from 22% to 53% of the subjects⁷⁻⁹; in contrast, in children with mastocytosis, Hymenoptera stings played no role in eliciting anaphylaxis.^{7,8}

Second, the association is also confirmed because the prevalence of CMD in patients with HVA is greater than in general population. As a matter of fact, according to the literature, between 1.0% and 7.9% of patients with HVA have a CMD (**Table 1**). The lower prevalence rate reported in some study could be explained by the low sensitivity of the screening test used,¹⁴ by the lack of a BM evaluation,¹⁵ or the evaluation of CD25/CD2 MC coexpression by flow cytometry and/or Kit mutation.¹⁶⁻¹⁸

Formerly, systemic or anaphylactic reactions after Hymenoptera stings were described in case reports or in a small series of patients with cutaneous mastocytosis or SM (**Table 2**).¹⁹⁻²²

The first report of a routine BM evaluation of patients with HVA and raised tryptase showed 7.9% of CMD among all the patients with systemic reactions to Hymenoptera venom, regardless of serum basal tryptase (SBT) level.²³ In this series, 88% of the patients who underwent BM evaluation (for SBT >11.4 ng/mL; n = 34) were diagnosed with a CMD: indolent SM (ISM) in 21 subjects (62.%), where 14 patients fulfilled both major and minor criteria, and 7 satisfied 3 minor criteria and MMAS in 9 subjects (26%). Therefore, 16 ISM/MMAS cases (47%) would not have been diagnosed without flow cytometry KIT mutation analysis, or both. Increased SBT seems to be a useful criterion for selecting patients eligible for BM evaluation when SM is suspected^{23,24},

Table 1
Prevalence of CMD in patients with. Systemic reactions to Hymenoptera venom, screened on the basis of elevated tryptase^a

	Patients	Raised Tryptase (%)	CMD	%
Haeberli et al, ¹⁵ 2003 ^b	259	19 (7.3)	3 CM	1
Dubois, ¹⁴ 2004 ^c	2375	32 (1.3)	22 SM	1
Rueff et al, ¹⁶ 2006 ^e	1102	106 (9.6)	21 CM + 8 SM	2.6
Bonadonna et al, ²³ 2009	379	44 (11.6)	21 ISM + 9 MMAS	7.9
Potier et al, ¹⁷ 2009 ^e	138	22 (15.9)	1 CM + 5 SM	4.4
Guenova et al, ¹⁸ 2010 ^{d,e}	274	30 (10.9)	1 CM + 3 ISM	1.5

Abbreviations: BM, bone marrow; CM, cutaneous mastocytosis; CMD, clonal mast cell disease; ISM, indolent systemic mastocytosis; MMAS, monoclonal mast cell activation syndrome; SBT, serum basal tryptase level; SM, systemic mastocytosis.

^a SBT > 11.4 ng/mL.

^b BM evaluation not performed.

^c Screening with urinary Histamine metabolite.

^d BM performed if SBT > 15 ng/mL.

^e Evaluation of CD25/CD2 MC coexpression and Kit mutation not performed or reported.

Table 2
Characteristics of the majority of reported MCD presenting systemic reactions to Hymenoptera sting

	Patients (n)	Diagnosis	Male/Female	Median Age, y (Range)	Tryptase <20 ng/mL, n (%)	Without Skin Involvement, n (%)
Müller et al, ²⁰ 1983	3	2 CM ^a + 1 SM	1/2	34 (32–50)	Not reported	0
Kors et al, ⁶⁶ 1993	5	2 ISM (–) 3 ISM (+)	0/5	49 (20–71)	Not reported	2 (40)
Fricker et al, ³³ 1997	10	7 CM ^a 3 SM	4/6	39 (29–51)	5 (50)	0
Oude Elberink et al, ²² 1997	2	2 ISM	0/2	44–43	Not reported	0
Dubois, ¹⁴ 2004	17	17 SM	—	—	—	8 (47)
González de Olano et al, ⁷ 2007	21	21 SM	17/4	50 (29–74)	2 (9)	16 (76)
Potier et al, ¹⁷ 2009 ^b	1 CM + 4 ISMs(+) 2 ISMs(–)	6/1	45 (29–59)	1 (14)	2 (28)	—
Bonadonna et al, ²³ 2009	30	21 SM 9 MMAS	13/8 9/0	48 (19–76) 51 (32–69)	6 (29) 6 (67)	26 (87)
Alvarez-Twose et al, ³⁴ 2014	150	143 ISMs(–) 7 ISMs(+)	111/32 —	44 (16–76) —	54 (38) —	143 (95)
Bonadonna et al, ¹⁰ 2016	219	171 ISMs(–) 48 ISMs(+)	—	—	—	171 (78)
Rietveld et al, ⁵⁷ 2016	9	4 ISMs(–) 5 ISMs(+)	05/04/18	52 (36–72)	—	4 (44)
Michel et al, ⁴⁷ 2016	27	5 CM 4 MIS 8 ISMs(+) 9 ISMs(–) 1 MMAS	1/4 3/1 4/4 3/6 1/0	44 (31–56) 39 (26–49) 61 (41–76) 55 (46–59) —	4 (80) 0 1 (12) 4 (44) 0	8 (30)
Total	500	15 CM 4 MIS 140 ISMs(+) 331 ISMs(–) 10 MMAS	184/87 (ratio 2.11)	—	90/238 (38)	380 (76)

Abbreviations: BM bone marrow; CM, cutaneous mastocytosis; CMD, clonal mast cell disease; ISM, indolent systemic mastocytosis; ISMs(–), indolent systemic mastocytosis skin negative; ISMs(+), indolent systemic mastocytosis skin positive; MMAS, monoclonal mast cell activation syndrome; SM, systemic mastocytosis.

^a BM evaluation not performed or in a portion of cases.

^b BM histology without evaluation of CD25/CD2 MC expression.

nevertheless, a CMD cannot be excluded in subjects with systemic severe HVA but with normal SBT.²⁵

In a retrospective analysis of 142 subjects without skin lesions who were investigated for suspected CMD, none of the 44 patients with a SBT of less than 10 ng/mL confirmed a diagnosis of CMD.²⁶

However, a failure to identify a CMD in patients with normal SBT could be possibly related to the technical approach used. In fact, BM MC immunophenotyping with only 300,000 events, as well as the KIT-D816 V mutation detection by techniques less sensitive than reverse transcriptase qualitative polymerase chain reaction cannot be sufficient to identify atypical MC in patients with very low MC burden. In a recent study, 22 patients with at least 1 episode of anaphylaxis with ascertained hypotension after Hymenoptera sting, normal SBT and the absence of urticaria pigmentosa underwent BM evaluation. The diagnosis of ISM was established in 16 patients and MMAS in 1 patient. Notably, in all cases the diagnosis of ISM was based only on minor criteria because BM biopsy specimens did not show compact MC aggregates.²⁷

Several years ago, a Spanish group identified 4 clinical elements (male sex, presyncope and/or syncopal episodes, absence of urticarial/angioedema, and serum tryptase >25 ng/mL) as independent predictive factors of CMD in patients suffering from insect bite anaphylaxis without mastocytosis in the skin.⁴ The evaluation of these parameters—the so-called REMA score—provides a good tool for screening patients with suspected mastocytosis for severe mediator symptoms but without typical skin lesions.²⁸ An early diagnosis of CMD in patients with normal tryptase and severe HVA would represent a substantial advantage for several reasons. One-quarter of these patients had evidence of osteoporosis²⁷ and early therapy can prevent vertebral fractures.²⁹ Some fatal sting reactions have been described in patients with SM with HVA after stopping VIT^{22,30}; thus, an accurate diagnosis is essential in recommending life-long treatment. Another category of patients with HVA has been shown very recently in which there is cause to suspect a CMD: those who experienced severe reactions at re-sting after VIT discontinuation³¹; as a matter of fact, the authors confirmed that 95% of these patients, when investigated thoroughly by the most sensitive available techniques, resulted to be affected by a CMD.

Clinical Characteristics of Patients with Hymenoptera Venom Allergy and Clonal Mast Cell Disease

For years, the diagnostic workup for SM in patients with HVA has been usually limited to those with urticaria pigmentosa, because cutaneous mastocytosis or SM with skin involvement was believed to represent the majority of these patients.^{16,20,22,32,33} Instead, in later years, it has been shown that HVA is more frequent in patients with mastocytosis without skin involvement^{7,10,23,34} (see [Table 1](#)).

Surprisingly, progression to aggressive mastocytosis or an associated hematologic malignancy has not been yet reported in patients with SM with HVA³⁵ and, as a consequence, HVA seems to be absent in patients with the aggressive subtypes of SM, who harbor the highest MC load.^{36,37}

It has been reported that patients with mastocytosis who experience anaphylaxis with 1 trigger do not react to others.⁹ This issue has been confirmed more recently, where 90% of ISM skin negative patients diagnosed after HVA do not refer anaphylaxis with other triggers.¹⁰

Another important characteristic of patients with HVA and ISM skin negative disease is the male predominance, a significantly lower MC burden, lower levels of serum tryptase, and a lower frequency of dense compact MC aggregates in BM sections than in ISM skin positive patients. They also frequently show coexisting populations of

phenotypically normal and aberrant MC in BM and a lower frequency of multilineage KIT mutation.^{4,28}

The majority of patients do not report MC activation symptoms between acute episodes; therefore, most of these patients may have HVA severe reactions as the sole clinical manifestation of mastocytosis.

The anaphylactic reactions of patients with CMD and HVA are characterized in most cases by the absence of angioedema and erythema, and the predominance of cardiovascular symptoms, such as hypotension, leading to loss of consciousness.^{27,34}

Management of Patients with Hymenoptera Venom Allergy and Clonal Mast Cell Disease

Diagnosis

The diagnosis of HVA is based on the combination of a history of reactions to stings and positive IgE antibodies, which can be revealed by intradermal testing with venom or by measurement of sIgE in serum.³⁸

Current guidelines indicate that the diagnostic tests should be performed only on patients who have suffered from anaphylactic reaction.^{13,38} In fact, asymptomatic sensitization to bee and wasp venom occurs frequently with in vitro tests, and 27.1% to 40.7% of the general population is reported to have detectable sIgE to Hymenoptera venom.^{39,40} One of the main causes of asymptomatic sensitization is the presence of sIgE to cross-reactive carbohydrate determinants in the serum^{41,42}; these carbohydrate structures are present in plants and invertebrates and IgE antibodies against cross-reactive carbohydrate determinants are found in patients allergic to pollen or insect venom. Nevertheless, a large portion of subjects sensitized to nonglycosylated venom allergens tolerate Hymenoptera stings well.

A recent study of a group of subjects who tolerated Hymenoptera sting and with detectable sIgE showed that only 5.3% of sensitized patients had severe systemic reactions (SSRs) after the sting challenge. These subjects presented a 9.5-fold higher risk than the general population for large local reactions but not for SSRs. Therefore, the frequency of reactors seems to be comparable with the risk of the general population and far less than the risk for a re-sting reaction in allergic patients, which was reported to be between 25% and 52% after deliberate sting challenges.⁴³

History

For an accurate diagnosis, it is important first to identify the culprit insect, even though there are numerous allergy-eliciting Hymenoptera species with overlapping phenotypes and, as a consequence, sometimes it is hard to discriminate between them; in fact, although it is easy to recognize the honey bee because it usually loses its stinger after sting or the *Vespa crabro* because it is very big and the nests are very typical, the same is not true in the case of wasps (yellow jacket and polistes), because they are very similar in shape and in behavior.

Tests

Skin tests, such as in vitro tests, should be done 4 weeks after the reaction; if negative, the test can be easily repeated because, in some cases, it becomes positive a few weeks later.⁴⁴ In contrast, if the time period between the sting and the test is longer, the result may be falsely negative.

In vivo tests

Skin prick tests are performed with a standard concentration of insect venom ranging from 1 to 100 $\mu\text{g/mL}$. If skin prick tests are negative, intradermal tests are then performed with concentrations of 0.001 to 1.000 $\mu\text{g/mL}$. Higher concentrations may

lead to false-positive results.⁴⁵ The extracts usually used for the all diagnostic procedures (in vivo and in vitro tests)³⁸ are *Apis mellifera*, *Vespa crabro*, *Polistes dominulus*, and *Vespula vulgaris*. In fact, is very important for a correct diagnosis and the subsequent prescription of immunotherapy, to include *Polistes dominulus*, which is largely diffused in Europe,¹² especially in the Mediterranean areas (Italy, Greece, Spain, France, and North Africa).

The safety of skin tests was confirmed in many studies, which did not report any reaction in patients with mastocytosis and HVA.^{7,23,45–47}

In vitro test

The first level test is the detection of sIgE against major natural allergens of venom (CAP assay). Thanks to modern molecular biology technology and the increasing knowledge about venom composition on a molecular level, in the last decade it has become possible to develop an advanced molecular or component-resolved diagnostics approach to HVA, which has largely contributed to solving many diagnostic challenges.⁴⁸ The detection of these recombinants allowed a more precise diagnosis with the identification of the causative venom in patients with apparent double sensitization to yellow jacket and wasp (*Polistes*) venom or to honeybee and yellow jacket venom.⁴⁹ The Hymenoptera venom allergens currently available on various diagnostic platforms are for honey bees (*Apis*; Api m 1, Api m 2, API m 3, Api m 4, Api m 5, and Api m 10), for yellow jacket (*Vespula vulgaris*; Ves v1, Ves V 5), and for European paper asp (*Polistes dominulus*; Pol d 1 and Pol d 5).

More recently, some authors used Ves v 1 and Ves v 5 (Immulite system) to diagnose 27 patients with yellow jacket venom allergy and 53 patients with yellow jacket venom allergy and mastocytosis and/or elevated baseline serum tryptase.⁴⁷ This study confirmed that the analyses of sIgE reactivity on a component-resolved level revealed no obvious differences in the reactivity profiles of Hymenoptera venom-allergic patients of 2 groups; in contrast, it showed that a diagnostic sensitivity of 100% was reached in the mastocytosis group using the recombinant allergens an the cutoff of 0.10 kUA/L, instead of the cutoff of 0.35 kUA/L. Other authors more recently confirmed in a study that, with the lower cutoff, the diagnostic sensitivity improved but specificity did not; therefore, they showed that the optimal combined diagnostic sensitivity and specificity of sIgE was found at a cutoff level of 0.21 kUA/L (82.1% and 87.5%, respectively). However, because missing the diagnosis of yellow jacket venom allergy could have serious consequences, a lower cutoff level of 0.17 kUA/L is preferable, which gives a sensitivity and specificity of 83.6% and 85.0%, respectively.⁵⁰

Basophil activation test

The basophil activation test (BAT) has been proposed as a useful adjunct in the diagnosis of allergic disease, especially in patients with negative or contradictory conventional tests.⁵¹ In the BAT, basophils are used as an in vitro model for MCs because both contain granules of preformed molecules that can cause an anaphylactic reaction after degranulation. Using the BAT, both IgE-mediated and IgE-independent type 1 hypersensitivity can be measured in vitro.⁵² In patients with HVA, the BAT was proposed as a third-level test for selected cases, and it can be useful in polysensitization patients.^{53–55} Regarding patients with mastocytosis, the role and usefulness of the BAT remains a topic of discussion in the current literature, with earlier studies reporting conflicting evidence. The first study, which evaluated the value of BAT in patients with mastocytosis,⁵⁶ confirmed that in 11 patients with SM who had specific sIgE against Hymenoptera venom and an evaluable BAT, BAT was found to be positive in 9 patients. Additionally, a positive BAT was detected in 3 of 7 patients who had

no sIgE. A further study that evaluated 7 patients with SM with reactions to Hymenoptera stings and negative tests confirmed that 6 of these patients with SM were also negative with the BAT; therefore, the authors confirmed that this test did not add valuable information, because it was invariably negative when the standard diagnostic tests were negative.⁴⁵ More recently, some authors evaluated 29 patients with SM, 9 of whom had a history of HVA, and sIgE was detected in 6 patients with HVA. The BAT was positive in only 1 patient, for whom the skin test and sIgE were also positive⁵⁷; therefore, the authors confirmed the data from previous study⁴⁵: the BAT is not a reliable tool for randomly screening patients with SM for HVA.

Based on these data from the literature, we therefore postulate that the BAT does not add useful information to the conventional diagnostic tests for HVA.

Immunotherapy

The only curative treatment that is effective in reducing the risk of subsequent systemic reactions and improving the patients' quality of life is VIT. VIT in the general population is reported to be effective in 77% to 84% of patients treated with honeybee venom and in 91% to 96% of patients receiving vespid venom.⁵⁸

After some debate, mainly owing to safety concerns,²² it is now generally accepted that VIT is clinically justified in those patients with severe HVA and documented mastocytosis. In fact, it is now generally accepted that VIT should be given always. Based on the data from the literature available to date, the effectiveness of treatment in patients with mastocytosis with standard doses is slightly lower than in the general population (Table 3). Recently however, more robust recommendations have been

Table 3 Immunotherapy in patients with mastocytosis				
Author	Diagnosis	Patients with Mastocytosis, n (%)		Cumulative Reactions to Re-sting, n/N (%)
		Total	Side Effects System	
Engler, ⁶¹ 1994	4 UP, 1 ISM	2 (33)	2 (33)	0/1
Fricker, ³³ 1997	3 ISM + UP, 3 ISM – UP +, 4 UP no BM diagnosis	2 (20)	1 (10)	1/6 (16)
Haeberli, ¹⁵ 2003	10 patients with tryptase >13.5 µg/L and sting challenge performed	1 (10)	1 (10)	4/10 (40)
Dubois, ¹⁴ 2004	7 SM	6 (85)	6 (85)	6/7 (85)
Rueff, ¹⁶ 2006	48 patients with mastocytosis	9 (18.8) built up phase of VIT	9 (18.8) built up phase of VIT	7/33 (21.6)
González De Olano, ⁷ 2007	21 ISM (5 UP+, 16 UP-)	6 (29) 3 built up, 3 maintenance phase of VIT	5 (24)	3/12 (25)
Bonadonna, ²³ 2009	16 ISM (2 UP+, 14 UP-)	2 (12.5)	0	2/13 (15)
Bonadonna, ⁴⁶ 2013	77 ISM (12UP+, 65 UP-) MMAS 7	10 (8.4)	4 (built up) (4.8)	7/50 (14)
Total	201	38 (18.9)	28 (13.9)	30/132 (22.7)

Abbreviations: BM bone marrow; ISM, indolent systemic mastocytosis; MMAS, monoclonal mast cell activation syndrome; SM, systemic mastocytosis; UP, urticaria pigmentosa; VIT, venom immunotherapy.

provided for the use of VIT in patients with SM and HVA. By joining together 2 homogeneous populations of patients from Italy and Spain, the authors had a relatively large number of patients with HVA and SM.⁴⁶ In this study, VIT was well-tolerated, although a slightly higher number of adverse events were seen with the rush-modified induction regimen. Thus, although a statistical significance was not seen, it would be reasonable to suggest a less aggressive induction in patients with SM. Despite previous reports,⁵⁹ none of the patients discontinued the treatment owing to VIT-related side effects, and no reaction was observed during the maintenance period. In addition, in patients with HVA and SM not fully protected at field re-stings, an increase of the maintenance dose to 200 µg of venom could be recommended.⁴⁶ The study also confirmed that VIT conferred a full protection in the majority (86%) of re-stung patients, although this percentage is slightly smaller than that reported in patients without SM.⁶⁰

Furthermore, in patients with mastocytosis, a pretreatment with an H1 antihistamine can be used to decrease the number and severity of large local reactions and mild SRs to VIT, such as urticaria and angioedema.^{13,61} More recently, several case reports showed that pretreatment with anti-IgE monoclonal antibodies may permit more rapid and higher doses of allergen immunotherapy: patients with ISM who experienced SRs to VIT were able to tolerate immunotherapy after pretreatment with omalizumab.^{35,62–65}

In the normal HVA population, the literature confirmed that a minimum of a 5-year treatment is better for long-term effectiveness⁵⁸ and life-long therapy should be considered in patients with severe initial SSRs, systemic adverse events during VIT, and patients allergic to honeybee venom allergic with a high risk of future honeybee stings. In the literature, there are some case reports showing that patients with mastocytosis and HVA, who were protected during VIT, can have very severe reactions after VIT discontinuation.^{22,66}

Very recently, some authors performed a retrospective multicenter study evaluating patients with HVA who underwent a 4- to 11-year course of VIT for previous severe reactions. For the analysis, they considered patients who experienced severe reactions at re-sting after VIT discontinuation. None of them had a previous ascertained diagnosis of mastocytosis, and in fact, in all but 1 tryptase evaluation was not performed before VIT because in that time (before 2007) tryptase dosage was not routinely evaluated.

Importantly, 95% of these patients were thoroughly investigated by the most sensitive available techniques and found to be affected by a CMD. The results obtained in these selected patients clearly documented that the probability of having mastocytosis (in any form) is quite high when VIT protection is lost after treatment. This finding would suggest that patients with HVA-induced anaphylaxis who lose protection after a proper course of VIT should be investigated for mastocytosis. These data also confirmed that, when a diagnosis of mastocytosis is established, these patients should continue life-long VIT³¹, therefore, from a practical point of view, regardless of the tryptase value, we would suggest an accurate hematologic workup be performed before stopping immunotherapy in those patients with very severe reactions with hypotension and without urticaria and angioedema to exclude CMD. In these patients, it is very important to use a highly sensitive multiparameter flow cytometry approach to stain BM cells, using a combination of 5 monoclonal antibodies—CD45, CD117, CD34, CD25, and CD2—and with at least 1 to 3 million events acquired to detect atypical MC in these patients who have a very low MC burden.²⁷

In general, to improve the compliance of patients in the HVA population who have to continue life-long injections, a 3- to 4-month extended interval can be proposed, and this schedule, adopted after 5 years of immunotherapy, seems to be safe and effective.⁶⁷ We can hypothesize that patients with mastocytosis can also adopt this

schedule even if up to now there have been no studies about the efficacy and protection in case of re-sting.

All patients with mastocytosis who undergo VIT, even in the maintenance phase, should carry epinephrine self-injectors because of the persistent risk of SSR and the possibility that SSR may also occur after a sting of an insect whose venom was not used for VIT.³⁰

Emergency treatment

Patients with CMD should carry with them an emergency kit irrespective of tests result. Moreover, patients with mastocytosis who have experienced SSRs should carry 2 or more epinephrine self-injectors. In a recent position paper from the European Academy, this precaution is also advised for all patients with mastocytosis treated with VIT, even if they had reached the maintenance dose.⁶⁸

KEY MESSAGES

- HVA represents the most common trigger of anaphylaxis in subjects with mastocytosis.
- The majority of patients with HVA and SM are diagnosed as SM lacking skin lesions and this is called BM mastocytosis.
- There is a strong association between Hymenoptera anaphylaxis with a negative allergy study and the presence of an underlying SM.
- Anaphylaxis manifestations in HVA and CMD are characterized by an absence of angioedema and erythema, and the predominance of cardiovascular symptoms.
- The characteristics of severe HVA episodes, with hypotension in the absence of urticaria and/or angioedema, may represent the most relevant factor in identifying those patients with HVA and CMD, regardless of baseline tryptase levels.
- In cases of systemic reaction after Hymenoptera sting in patients with CMD, it is mandatory to perform *in vivo* and *in vitro* tests to identify the culprit insect venom and then start correct immunotherapy, which must be continued for life.
- The only therapy effective in patients with HVA and CMD is immunotherapy, which is generally well-tolerated. VIT must be continued for life.
- The probability of having SM (in any form) is quite high when VIT protection is lost after treatment. It can be hypothesized that patients with no skin involvement, normal SBT levels, and anaphylaxis with certain hypotension and loss of consciousness caused by Hymenoptera stings should undergo a BM examination to detect a possible CMD before stopping immunotherapy.

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