

Hymenoptera Allergy and Mast Cell Activation Syndromes

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Abstract Mast cell activation syndrome (MCAS) can be diagnosed in patients with recurrent, severe symptoms from mast cell (MC)-derived mediators, which are transiently increased in serum and are attenuated by mediator-targeting drugs. When KIT-mutated, clonal MC are detected in these patients, a diagnosis of primary MCAS can be made. Severe systemic reactions to hymenoptera venom (HV) represent the most common form of anaphylaxis in patients with mastocytosis. Patients with primary MCAS and HV anaphylaxis are predominantly males and do not have skin lesions in the majority of cases, and anaphylaxis is characterized by hypotension and syncope in the absence of urticaria and angioedema. A normal value of tryptase (≤ 11.4 ng/ml) in these patients does not exclude a diagnosis of mastocytosis. Patients with primary MCAS and HV anaphylaxis have to undergo life-

long venom immunotherapy, in order to prevent further potentially fatal severe reactions.

Keywords Systemic mastocytosis · Mast cell activation syndromes · Hymenoptera venom allergy · Anaphylaxis · Tryptase · Clonal mast cell activation syndromes

Introduction

Mast cell activation (MCA) occurs in a number of different clinical conditions, including IgE-dependent allergies, other inflammatory reactions, and mastocytosis, a group of clonal disorders of the mast cell (MC) lineage. MCA-related symptoms may be mild, moderate, severe, or even life threatening. The severity of MCA depends on genetic predisposition, the number and releasability of MC involved in the reaction, the type of allergen, the presence of specific IgE, and the presence of certain comorbidities. In severe reactions, MCA can be documented by a substantial increase of serum tryptase level above baseline. When symptoms are recurrent, accompanied by a transient increase in MC-derived mediators in biological fluids, and are responsive to treatment with MC-stabilizing or mediator-targeting drugs, the diagnosis of mast cell activation syndrome (MCAS) is appropriate [1•]. Hymenoptera venom allergy (HVA) is a typical IgE-mediated reaction due to sensitization to one or more allergens of the venom, and accounts for 1.5–34 % of all cases of anaphylaxis [2]. In recent years, a preferential association between HVA and mastocytosis was highlighted [3•]. Therefore, patients with both diseases represent a population requiring a specific management.

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Mast Cell Activation Syndrome Classification

MCAS can be diagnosed when patients have recurrent systemic, usually severe, symptoms of MC activation, and involvement of MC can be documented preferably by demonstrating a transient increase of serum tryptase or another established MC mediator during (or shortly after) an event; moreover, symptoms need to respond to anti-mediator-type or MC-stabilizing medications [1•, 4, 5]. All these criteria should be fulfilled in order to confirm the diagnosis of MCAS.

Recently, three distinct MCAS categories have been defined as follows:

- i. Primary (clonal) MCAS, when KIT-mutated, clonal MC are detected: this category includes true mastocytosis (according to WHO criteria, see below) and cases not fulfilling sufficient criteria for systemic mastocytosis (SM) but showing MC clonality markers, preferentially KIT mutation. These latter patients may have a limited, pre-diagnostic form of SM, also indicated as monoclonal mast cell activation syndrome (MMAS), but their risk of developing severe life-threatening anaphylaxis is similar to patients with true SM
- ii. Secondary MCAS, when there is an underlying inflammatory disease, often an IgE-dependent allergy, but no KIT-mutated MC are demonstrable
- iii. Idiopathic MCAS, when neither MC clonality or MCA triggers are identified.

In some patients primary and secondary forms may sequentially occur, and a primary MC disorder does not exclude the presence of a coexisting allergy or vice versa. Some patients affected from primary MCAS may develop a severe anaphylaxis due to an underlying allergy (for example HVA and/or drug and/or food allergy) [1•].

Systemic Mastocytosis

Mastocytosis is a heterogeneous group of clonal diseases, characterized by proliferation and accumulation of MC in different tissues, mainly skin and bone marrow (BM) [6]. Cutaneous mastocytosis (CM), characterized by the sole involvement of the skin, is typical in infants, while systemic disease (SM) is more common in adults and involves at least one extracutaneous organs (BM, gastrointestinal tract, lymph nodes, and spleen), with or without skin involvement. The majority of cases of SM are associated to a somatic “activating” point mutation [7] at codon 816 of KIT-receptor gene, but other uncommon somatic and germ-line mutations have been reported, most frequently in individual cases [7].

Diagnosis and classification of mastocytosis are based on the identification of neoplastic MC by their morphological,

immunophenotypic, and molecular characteristics based on well-established WHO criteria [6]. The diagnosis of SM is made upon the presence of the major criterion (histological finding of at least 15 multifocal dense MC infiltrates in BM or other extracutaneous organs) plus 1 minor criterion, or at least 3 out of 4 minor criteria (abnormal morphology of extracutaneous MC; serum tryptase >20 ng/ml; expression of CD2 and/or CD25 on BM MC; detection of a mutation at codon 816 of the *KIT* gene in extracutaneous organs) [6]. Clinical features associated with MC burden (B findings) or aggressiveness of disease (C findings) are also applied to subclassify patients with SM.

Some patients display symptoms of MC mediators release but do not strictly fulfill the WHO criteria for SM, despite having KIT-mutated clonal MC and usually expressing CD25 on BM MC: the cases were defined with various terms including MMAS [1•, 8, 9], and clonal MC activation disorders (c-MCAD) [10, 11]. MMAS has been diagnosed in patients with systemic reactions to Hymenoptera stings as well as in patients with unexplained episodes of anaphylaxis [9, 12–16].

The clinical picture of mastocytosis is extremely heterogeneous, ranging from asymptomatic disease to a highly aggressive course with multisystemic involvement. In patients with indolent disease, symptoms result from the local or remote effects of mediator release from MC, such as histamine, proteases, leukotrienes, and prostaglandins. These so-called MC mediator-related symptoms include flushing, pruritus, palpitations, dizziness, hypotension, syncope, breathing difficulties, abdominal pain, nausea, vomiting, diarrhea, headache, sweating, lethargy, fatigue, lack of concentration, irritability, anxiety, depression, arthralgia, and myalgia [17]. Symptoms may either occur in a scattered way or a constellation of symptoms may resemble an anaphylactic reaction, which might be life threatening as in the appearance of anaphylactic shock.

Clonal MCAS and Anaphylaxis

The prevalence of anaphylaxis in mastocytosis patients is much higher than the 0.05–2 % estimated frequency of anaphylaxis in the general population [18, 19]. Indeed, it has been reported between 22 and 49 % in adults [20–22] and between 6 and 9 % in children [20, 21]: discrepancies among different studies might be a result of the heterogeneity of patient cohorts, the definition of anaphylaxis, and the sensitivity of diagnostic techniques.

The frequency of anaphylaxis in patients with indolent SM who have skin lesions [ISMs(+)] is lower than in ISMs(–): Alvarez-Twose et al. reported a history of anaphylaxis characterized by hypotension in more than 90 % of ISMs(–), while only 28 of their 114 ISMs(+) patients (24.5 %) presented an anaphylactic episode [10].

A wide variety of stimuli (venom, drug, 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, the term “idiopathic anaphylaxis” is used.

It has been reported that mastocytosis patients who experience anaphylaxis with one trigger do not react with others [22]. This is confirmed also in our experience: noteworthy, 90 % of our ISMs(−) patients diagnosed after HVA do not refer anaphylaxis with other elicitors (Table 1).

Hymenoptera Venom Allergy and Clonal MCAS

Hymenoptera stings represent the most common trigger of anaphylaxis in subjects with clonal MCAS (c-MCAS) [20–22]. On the other hand, the frequency of c-MCAS in subjects with HVA ranged from 1 to 7.9 %: the lower prevalence reported in some studies may be explained by the low sensitivity of screening tests or by the lack of a comprehensive BM evaluation, including flow cytometry and sensitive KIT mutation detection [3•].

The association between HVA and c-MCAS was initially described mainly in patients with urticaria pigmentosa [23–25], but HVA is more frequent in patients without skin involvement from mastocytosis [11, 12, 26–29].

We reported for the first time results of routine BM evaluation in patients with HVA and raised tryptase, identifying a percentage of c-MCAS as high as 7.9 % [12]. In that series, 20 % of cases of ISM or MMAS would not have been diagnosed without the “minor criteria” of flow cytometry, KIT mutation analysis, or both. In an update of our series including 414 SM and 20 MMAS, more than half of patients suffered from a systemic reaction to HV (Fig. 1).

Patients with HVA and c-MCAS without skin involvement are predominantly males and they display significantly lower MC burden, lower levels of serum tryptase, and lower frequency of dense compact MC aggregates in BM sections than ISMs(+) patients. They also frequently show coexisting

populations of phenotypically normal and aberrant MC in the BM, and a lower frequency of multilineage KIT mutation [10, 11]. The majority of patients do not report MCA symptoms between acute episodes. Therefore, the majority of these patients may have HVA severe reactions as the sole clinical manifestation of mastocytosis.

Anaphylactic reactions are characterized in the majority of cases by absence of angioedema and erythema and predominance of cardiovascular symptoms, such as hypotension leading to loss of consciousness [11, 22, 30].

The Spanish group identified that four clinical elements (male sex, presyncopal and/or syncopal episodes, absence of urticaria/angioedema, and serum tryptase >25 ng/ml) are independent predictive factors of having a clonal systemic MC disease in patients suffering from insect bite anaphylaxis without mastocytosis in the skin. The evaluation of these parameters—the so-called REMA score—provides criteria for BM examination, in order to maximize the chance of finding a c-MCAS [10].

In our first study, only patients with systemic reaction to HV and raised basal tryptase levels underwent BM examination, but recently, we showed that also patients with normal basal tryptase and HVA characterized by hypotension are at high risk to have c-MCAS [31••]. In this last series, tryptase values ≥ 7.95 ng/ml seem to be associated to the risk of SM with the highest values of sensitivity and specificity, above all when severe anaphylaxis occurred without skin symptoms. These results raise issues about the role of clonal CD25⁺ MC bearing activating mutations in c-kit (which appear to result in a hyper-responsive MC phenotype) as biomarkers for severe systemic reaction after Hymenoptera sting. Nowadays, we suggest that patients who have HVA presenting with hypotension and loss of consciousness without urticaria and angioedema during the anaphylactic reaction worth a BM examination to detect a possible c-MCAS, even in case of normal serum tryptase. These patients have a very low MC burden, and the BM study should be necessarily performed in Reference Centers for MC diseases, using highly sensitive and adequate techniques.

Table 1 Incidence of anaphylaxis induced by other elicitors in 235 patients with MMAS and ISM with systemic reaction after Hymenoptera sting as a presenting symptom (data from GISM of Verona, unpublished data)

	MMAS, n (%)	ISMs(−), n (%)	ISMs(+), n (%)
No other elicitors (HVA only)	15 (93.7)	154 (90.1)	40 (83.3)
Drug	0	7 (4.1)	6 (12.5)
Drug and food	0	1 (0.6)	1 (2.1)
Food	0	3 (1.7)	0
Idiopathic	1 (6.3)	3 (1.7)	1 (2.1)
Diptera sting	0	3 (1.7)	0
Total	16	171	48

MMAS monoclonal mast cell activation syndrome, ISMs(−) indolent systemic mastocytosis without skin involvement, ISMs(+) indolent systemic mastocytosis with skin involvement, GISM Gruppo Interdisciplinare per lo Studio della Mastocitosi

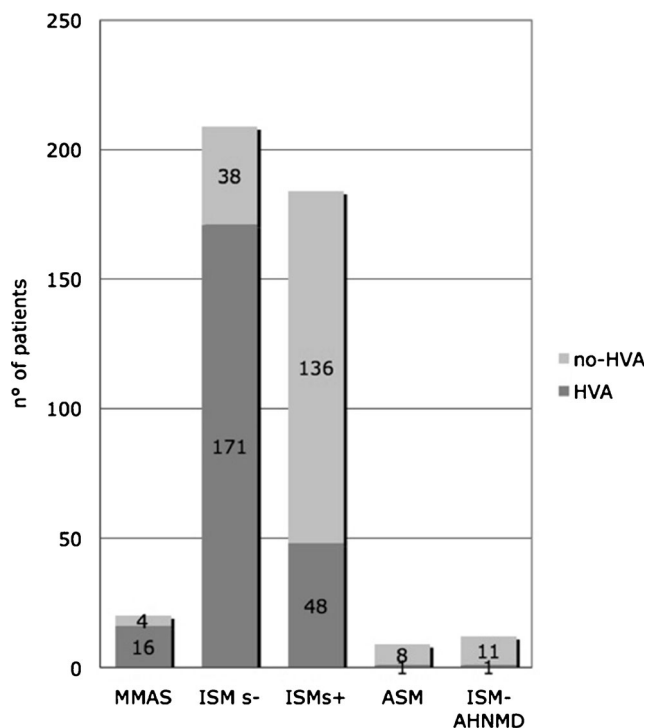


Fig. 1 Incidence of HVA in different variants of systemic mastocytosis (SM) and in monoclonal mast cell activation syndrome (MMAS) in our series of 434 patients. No patient initially presenting with hymenoptera anaphylaxis progressed to ASM; however, 1 patient with ISMs(−) and HVA developed a chronic myeloid leukemia and 1 patient with MMAS developed a myelofibrosis after 4.5 and 7 years from mastocytosis diagnosis, respectively. *ISMs(−)*: indolent systemic mastocytosis without skin lesions. *ISMs(+)*: indolent systemic mastocytosis with skin lesions. *ASM*: aggressive systemic mastocytosis. *ISM-AHNMD*: indolent systemic mastocytosis-associated clonal hematological non-mast cell disease

Surprisingly, HVA seems to be absent in patients with the aggressive subtypes of SM, who harbor the highest mast cell load [32, 33] and progression to aggressive mastocytosis or an associated hematological malignancy in patients with SM initially presenting with HVA has not been reported yet [34].

Management of Patients with Clonal MCAS and HVA

There are some arguments in the management of patients with c-MCAS and HVA. First of all, the effectiveness of immunotherapy depends on the correct identification of Hymenoptera venom allergen and an incorrect choice of immunotherapy does not protect from further sting reactions and, in some cases, a development of new sensitization.

Other important points are to confirm the safety of immunotherapy, understand which patients are candidate to these treatment and how long they have to undergo.

Another matter of debate is whether patients with c-MCAS always have to bring with them the emergency kit, regardless of fact they are undergoing to immunotherapy or not.

Diagnosis of HVA

HVA is a typical IgE-mediated reaction due to sensitization to one or more allergens of the venom, and accounts for 1.5–34 % of all cases of anaphylaxis [2]. The severity can vary from large local reactions (a swelling greater than 10 cm lasting up to 24 h) to systemic anaphylaxis, the most severe reaction which can occur. According to Mueller, the reactions are classified into 4 degrees of increasing severity [35].

The diagnosis of HVA is based on combination of a history of reactions to stings and positive IgE antibodies which may be revealed by intradermal testing with venom or by measurement of specific IgE in serum [36]. The diagnosis is easy when a patient has recognized the culprit insect, for example, because of the loss of the stinger (typical of honey bees) and there is a positive result to intradermal test with the corresponding venom. However, in most patients, the recognition is uncertain and skin tests show multiple positive results, making difficult the choice of venom to be used for specific immunotherapy.

Indication for the Diagnosis of Insect Venom Allergy

Current guidelines indicate that the diagnostic tests should be performed only in patients who suffered an anaphylactic reaction in their medical history [36, 37]. In fact, asymptomatic sensitization (AS) to bee and wasp venom occurs frequently in *in vitro* tests, and 27.1 to 40.7 % of the European general population is reported to have detectable specific IgE (sIgE) to Hymenoptera venom [38, 39]. Furthermore, AS is related to total IgE (tIgE) levels: in healthy subjects with high tIgE levels, sIgE to Hymenoptera venoms was demonstrable in up to 66.7 % of investigated subjects [39]. One of the main cause of AS is the presence of sIgE against cross-reactive carbohydrate determinants (CCDs) in the serum [40, 41]: these carbohydrate structures are present in plants and invertebrates and IgE antibodies against CCDs 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 showed that only 5.3 % of patients sensitized to Hymenoptera sting and with detectable sIgE had severe systemic reactions (SSRs) after a sting re-challenge. As compared to the general population, these subjects presented a 9.5-fold higher risk for large local reactions (LLRs) 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 between 25 and 52 % after deliberated sting challenges [42].

Although there was a considerable progress in the development of diagnostic tools, such as the basophil activation test (BAT) and component resolve diagnosis, it is still not possible to use in vitro tests to differentiate between AS, LLRs, and SSRs. Since the current guidelines of the European Academy of Allergy do not advice to treat the patients with positive skin test or sIgE who were not stung or tolerated the sting, diagnostic tests have to be performed only in subjects who suffered an anaphylactic reaction to an insect sting and therefore are candidates to immunotherapy. Up to now, this approach is recommended also for mastocytosis patients even though more studied are mandatory to determine if in such patients an early diagnosis could be useful in view of a prophylactic treatment.

Diagnostic Tests

These include the in vivo (prick test and intradermal test) and in vitro (serological) tests. Generally, guidelines recommend sIgE determination and skin testing not earlier than 2 weeks after the sting because sIgE levels could be decreased or even undetectable. If negative, tests can be easily repeated and in some cases they become positive few weeks later [36, 43].

For both skin test and measurement of sIgE, the extract of all available Hymenoptera venom should be used, including *Polistes dominulus* (PD), which is largely diffused in Europe [44], especially in the Mediterranean areas (Italy, Greece, Spain, France, and North Africa). PD is different from American species (AP) that are not present in Europe and some studies show that American and European species of *Polistes* are phylogenetically distant. Therefore, the diagnostic workup for Hymenoptera sting should always include PD, at least in the Mediterranean areas, as the AP mix may lead to a false negative result [45].

- In vivo test: Skin prick tests are performed with the standard concentration of insect venom ranging from 1 to 100 mcg/ml. If skin prick tests are negative, intradermal tests are then performed with concentrations of 0.001 to 1 mcg/ml. Higher concentrations may lead to false positive results [46]. Skin testing are usually safe in patients with c-MCAS [46]; nevertheless, a close medical supervision and the immediate availability of the resuscitation facilities (intravenous access, the possibility of immediate administration of epinephrine, fluids, oxygen, steroids, and antihistamine drugs) are recommended [46, 47].
- In vitro test: The first level test is the detection of specific IgE against major natural allergens of venom (CAP assay). Thanks to modern molecular biology technology, in the last decade it has become possible to determine the presence of sIgE against purified and recombinant allergens

[48], such as Api m 1 and Api m 10 from honey bee venom, Ves v 5 from yellow jacket venom, Pol d 5 from wasp venom, and also CCD. 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].

Other available techniques include CAP-inhibition assay and basophil activation test (BAT); of note, these are more expensive, time-consuming, and difficult to interpret.

It is well known that there is an association between Hymenoptera anaphylaxis with a negative allergy study and the presence of an underlying SM [12, 50–52]. This phenomenon has been attributed to an increased absorption of circulating IgE by a large amount of mast cells [53], or to a direct activity of Hymenoptera venom [54]. Several reports suggest that the absence of sensitization is more frequent in patients with mastocytosis [26]. These patients represent a diagnostic dilemma because choosing the extract to be used in case of negative tests is tricking, and diagnostic sting challenge would not be ethical, since its negative predictive value is low. Since patients with negative standard tests who exhibited a sensitization in cellular tests have been described, basophil histamine release test could be a suitable diagnostic option in skin test-negative patients with mastocytosis [25, 50].

The data on BAT in patients with negative skin test and serum IgE vary in different centers. An Italian study showed that negative standard test are reliable and BAT did not add useful information [46]. Other studies reported the usefulness of the method in false-negative patients with a sensitivity reaching 81–87 % in patients with mastocytosis [55, 56].

On the other hand, sIgE levels generally decrease in the long term after a sting [57, 58]; therefore, if the allergic reaction in mastocytosis patients occurred many years before, the negativity of test could depend from this physiologic decrease and it could be useful to repeat further tests in order to detect a possible sensitization.

Therapy

The therapy of patients with HVA and c-MCAS includes drugs for emergency and immunotherapy.

Drugs for Emergency

Intramuscular adrenaline is as first-line treatment of anaphylaxis and it must be used before instituting other interventions. Adrenaline is the only drug able to contrast the hypotension. This concept has to be clearly illustrated to patients and their doctors, because a delay on adrenaline administration can be fatal [59]. This drug must be administered not only to all

patients experiencing anaphylaxis but also in patients who have clinical features that are likely to evolve into anaphylaxis. Patients must use antihistamines and the steroids only after adrenaline, because antihistamines only relieve the cutaneous symptoms.

Patients with c-MCAS are more prone to anaphylaxis episodes especially after Hymenoptera sting; therefore, they should carry with them an emergency kit irrespective of test results. Moreover, patients with mastocytosis who have experienced SSRs should carry two or more epinephrine self-injectors. In the recent position paper of European Academy, this is also advised for all mastocytosis patients treated with venom immunotherapy (VIT), even if they had reached the maintenance dose [18].

When prescribing epinephrine, it is very important to explain to patients and relatives how and when to use the auto-injector, by simulating the self-administration, and also to schedule annual retraining of its use. This point is of huge importance and all efforts for a correct education of patients and their families should be carried out, because there are still reports that show how many patients are unable to properly use the adrenaline auto-injector in case of anaphylaxis for many reasons (miss to carry the auto-injector, fail to recognize symptoms, fear to use adrenaline or not trained to use the device) [60, 61].

Immunotherapy

VIT is recognized as a life-saving treatment for HVA patients. After some debate, mainly due to safety concerns [24], it is now generally accepted that VIT should be anyway given. As a matter of fact, it was also suggested that VIT may be safe and effective also in patients with HVA and SM [8, 27]. Recently, more robust recommendations were provided for the use of VIT in patients with SM and HVA, based on a large dataset [47]. In this study, VIT was well tolerated, although a slightly higher number of adverse events was seen with the rush-modified induction regimen. Thus, despite a statistical significance was not achieved, it would be reasonable to suggest a less aggressive induction in patients with SM. At variance with previous reports [62], none of the patients discontinued the treatment due to VIT-related side effects, and no reaction was observed during the maintenance period. Another relevant aspect is that VIT conferred a full protection in the vast majority of patients, as observed in patients without SM [63] and in patients receiving an extended maintenance regimen [64].

Although component resolved diagnosis is not recommended at present time, patients who are not protected with standard immunotherapy should be evaluated for minor components such as Api 10 or others [65].

A recent review showed that the incidence of side effects during VIT in mastocytosis patients was around 18.9 % [3], with a large variation (0–46 %), similar to the normal

population: generally vespid VIT was tolerated better (0–15 % of side-effects) than honeybee VIT [66].

Pretreatment with a H1 antihistamine reduces the number and severity of LLRs and mild SRs to VIT, such as urticaria and angioedema, both in normal population and in mastocytosis patients [37, 67]. De Olano et al. considered VIT in mastocytosis patients as a risky procedure, and they used premedication (oral disodium cromoglicate) and intensive care unit or monitored setting with management for resuscitation in all patients [20].

More recently, several case reports showed that a pretreatment with anti-IgE monoclonal antibodies may permit more rapid and higher doses of allergen immunotherapy: ISM patients who experienced SRs to VIT were able to tolerate it following pretreatment with omalizumab [68, 69].

No data on the long-term efficacy of VIT in mastocytosis patients are available. However, fatal cases occurred in patients who were stung after discontinuing VIT: in details, one patient died when stung 4 years after a 5-year course of VIT, and another died 6 months after a 2.5-year course of VIT [54]. In our center, we evaluated 6 patients who developed SSRs to HV after discontinuation of 5-years course of VIT and all were found affected by primary MCAS. Again, it has to be underlined the importance of a full hematological characterization in all patients presenting with HVA features suggestive for an underlying c-MCAS, even in the presence of not so elevated serum tryptase levels.

In order to better improve the compliance of patients who have to continue the injections lifelong, a 3–4-month extended interval can be proposed, since this maintenance schedule, adopted after 5 years of immunotherapy, is safe and effective. However, the dose interval cannot be extended indefinitely and, for example, a 6-month interval was found to be inadequate [64]. All VIT-treated mastocytosis patients, 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 [70].

Conclusions

The occurrence of c-MCAS in patients with HVA is now well ascertained, but probably still underestimated. In particular, HVA represents one of the most frequent clinical presentations in indolent SM without skin lesions.

The diagnosis of c-MCAS is of paramount clinical relevance to establish proper duration of VIT, which can protect the patient from other serious or even fatal reactions. A precise diagnosis of the culprit insect is mandatory in patients with mastocytosis who suffered from HVA. If the results are negative, procedures like skin tests and sIgE analysis should be repeated. If still, the result is negative, the BAT and

recombinant allergens increase the sensitivity and lead to the correct diagnosis in the majority of cases.

Allergen immunotherapy is the only causative treatment of insect venom allergy. The effectiveness of the treatment in mastocytosis patients with standard dose is slightly lower than in general population. Lifelong treatment is recommended in subjects with a diagnosis of primary MCAS.

Some aspects still remain unclear, such as why some patients with SM develop anaphylaxis following insect stings, while others do not, or why many patients react only to stings of one genus of Hymenoptera and tolerate others.

Take Home Message

- HVA represents the most common trigger of anaphylaxis in subjects with mastocytosis.
- HVA patients rarely refer anaphylaxis with other elicitors.
- The phenotype of patients with c-MCAS and severe HVA is characterized by the following:
 - Male sex
 - Absence of skin lesions in the majority of cases
 - Not very high basal tryptase levels
 - Syncope and hypotension with absence of urticaria and angioedema
- The normal value of tryptase (≤ 11.4 ng/ml) in patients with HV anaphylaxis does not exclude a c-MCAS; therefore, these patients, in absence of cutaneous lesions, have to undergo an hematological procedure if they have an anaphylaxis characterized by severe hypotension without urticaria and angioedema.
- In case of systemic reaction after Hymenoptera sting in patients with c-MCAS, it is mandatory to perform in vivo and in vitro tests to identify the culprit insect venom and then to start a correct immunotherapy which must to be continued lifelong.
- It is important to confirm the diagnosis of c-MCAS in patients with HVA:
 - Before to decide to stop VIT because, in patients with a diagnosis of c-MCAS, VIT must be continued lifelong
 - In order to give them a proper advice on the use of adrenaline
 - To investigate and manage other manifestations of c-MCAS, such as osteoporosis

Compliance with Ethical Standards

Conflict of Interest Dr. Bonifacio reports grants from Novartis Farna and personal fees from Ariad Pharmaceuticals and Amgen. Drs. Bonadonna, Bonifacio, Lombardo, and Zanotti declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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