

Anaphylactic Reactions After Discontinuation of Hymenoptera Venom Immunotherapy: A Clonal Mast Cell Disorder Should Be Suspected



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What is already known about this topic? There are no data on the presence and prevalence of mastocytosis in patients who experience severe reactions from Hymenoptera stings after the termination of an effective venom immunotherapy (VIT) course.

What does this article add to our knowledge? Mastocytosis should be suspected in those patients with Hymenoptera allergy who experience severe reactions and anaphylaxis after stopping VIT that had been previously protective.

How does this study impact current management guidelines? A proper diagnostic procedure for mastocytosis should be considered in patients developing severe reactions at re-sting after VIT discontinuation. VIT should therefore be continued lifelong in subjects with mastocytosis and venom allergy.

BACKGROUND: Up to 75% of patients with severe anaphylactic reactions after Hymenoptera sting are at risk of further severe reactions if re-stung. Venom immunotherapy (VIT) is highly effective in protecting individuals with ascertained

Hymenoptera venom allergy (HVA) and previous severe reactions. After a 3- to 5-year VIT course, most patients remain protected after VIT discontinuation. Otherwise, a lifelong treatment should be considered in high-risk patients (eg, in mastocytosis). Several case reports evidenced that patients with mastocytosis and HVA, although protected during VIT, can re-experience severe and sometimes fatal reactions after VIT discontinuation.

OBJECTIVE: To evaluate whether patients who lost protection after VIT discontinuation may suffer from clonal mast cell disorders.

METHODS: The survey describes the characteristics of patients who received a full course of VIT for previous severe reactions and who experienced another severe reaction at re-sting after VIT discontinuation. Those with a Red Española de Mastocitosis score of 2 or more or a serum basal tryptase level of more than 25 ng/mL underwent a hematological workup (bone marrow biopsy, KIT mutation, expression of aberrant CD25) and/or skin biopsy.

RESULTS: Nineteen patients (mean age, 56.3 years; 89.5% males) were evaluated. All of them had received at least 4 years of VIT and were protected. After VIT discontinuation they were re-stung and developed, in all but 1 case, severe anaphylactic reactions (12 with loss of consciousness, in the absence of urticaria/angioedema). Eighteen patients (94.7%) had a clonal mast cell disorder, 8 of them with normal tryptase.

CONCLUSIONS: Looking at this selected population, we suggest that mastocytosis should be considered in patients developing severe reactions at re-sting after VIT discontinuation and, as a speculation, patients with mastocytosis and HVA

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Abbreviations used

BM- bone marrow
BMM- bone marrow mastocytosis
CM- cutaneous mastocytosis
CMD- clonal mast cell disorder
HVA- Hymenoptera venom allergy
ISM- indolent systemic mastocytosis
MC- mast cell
SBT- serum basal tryptase
SM- systemic mastocytosis
VIT- venom immunotherapy

should be VIT-treated lifelong. © 2017 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1368-72)

Key words: Systemic mastocytosis; Hymenoptera venom allergy; Anaphylaxis; Re-sting; Tryptase

Systemic mastocytosis (SM) is a heterogeneous hematological disease characterized by the proliferation and accumulation of mast cells (MCs) in various tissues, with a preferential localization in bone marrow (BM) and skin.¹ Mastocytosis can be defined as cutaneous (CM) when confined to the skin and as systemic (SM). The diagnosis of SM requires the presence of the major criterion (multifocal dense MC infiltrates in BM or other extracutaneous organs) plus 1 minor criterion or 3 minor criteria: abnormal morphology of extracutaneous MC (spindle-shaped cells), increased serum basal tryptase (SBT) level of more than 20 ng/mL, expression of CD25 and/or CD2 on BM MC, and detection of a KIT mutation at codon 816 in extracutaneous organs. The most common presentation of SM is indolent systemic mastocytosis (ISM), but other less frequent forms are now recognized: smouldering SM, SM with associated hematologic neoplasia, aggressive SM, MC leukemia, and MC sarcoma.² Of note, patients with mediator-related symptoms not fulfilling the World Health Organization (WHO) criteria for SM, but carrying KIT-mutated and/or CD25-positive clonal BM MC, are considered as having a clonal mast cell disorder (CMD) defined also as (mono)clonal mast cell activation syndrome.^{3,4}

A preferential association between Hymenoptera venom allergy (HVA) and SM is now recognized,⁴⁻⁷ probably because Hymenoptera sting can be a trigger for anaphylactic reactions in patients with mastocytosis, who are “per se” prone to release mediators. HVA is associated in many cases to ISM without skin involvement, which is also defined as BM mastocytosis (BMM), a provisional SM variant still unrecognized by the WHO classification.^{1,2,4,7-9}

Venom immunotherapy (VIT) is effective in protecting most patients with HVA, even after its discontinuation. Nonetheless, we observed that a small proportion of patients, with previous severe reactions, lost the acquired protection when VIT was discontinued. Thus, we studied these patients to assess whether an unrecognized MC-related disorder was present.

METHODS

Patients and diagnosis

Patients referred to the Verona Multidisciplinary Outpatients Clinics for Mastocytosis from a nationwide network of allergists

between January 2009 and May 2014 were included in this survey. All had been diagnosed with HVA according to guidelines¹⁰ and underwent a 4- to 11-year course of VIT for their previous severe reactions. We considered for the analysis patients who experienced severe reactions at re-sting after VIT discontinuation. None of them had a previous ascertained diagnosis of mastocytosis. A basal tryptase evaluation was not performed before VIT because before 2007 the test was not available routinely. All patients provided their informed consent for allergy and hematological assessments, as per the standard diagnostic procedures adopted in our hospital. The institutional ethical committee was notified, but no formal approval was required for this observational, noninterventional study; all procedures were part of the standard of care.

At baseline, before VIT prescription, patients underwent the standard workup for the diagnosis of HVA.¹⁰ Skin test was performed with commercial extracts of *Polistes dominulus*, *Vespa crabro* (Anallergo Diagnostics, Florence, Italy), *Vespula* species, and honeybee (*Stellergenes Greer*, Antony, France). Four venom concentrations (100 µg/mL for prick test and 0.02 mL of 0.01, 0.1, and 1.0 µg/mL for intradermal test) were used, plus a negative control (NaCl 0.9%) and a positive control (histamine dihydrochloride 10 mg/mL). Serum-specific IgE for the same venoms and serum tryptase were always assayed by the ImmunoCAP test (Thermo Fischer Scientific Inc, Uppsala, Sweden) at least 2 weeks after an acute episode. The REMA score, proposed by the Red Española de Mastocitosis and based on 4 clinical/laboratory parameters (male sex, SBT > 25 ng/mL, presence of hypotension, and absence of angioedema/urticaria), was applied to predict the risk of CMD.⁴

All patients who experienced a systemic reaction at re-sting after VIT discontinuation with a REMA score of 2 or more or an SBT of more than 25 ng/mL were assessed for the presence of SM according to the diagnostic algorithm proposed by the European Competence Network on Mastocytosis.^{4,11} Thus, they underwent a dermatological evaluation to identify skin lesions, and a skin biopsy of suspected lesions was performed. A complete BM evaluation, including smear and biopsy, detection of D816V mutation of KIT, and flow cytometry,¹²⁻¹⁴ was also carried out. For the analysis of MC immunophenotype, we used a highly sensitive multiparameter flow cytometry approach, as previously reported. Briefly, BM cells were stained using a combination of 5 monoclonal antibodies, CD45, CD117, CD34, CD25, and CD2, and up to 6×10^6 cells per sample were acquired using a FACSCanto cytometer (BD, Becton Dickinson, Milan, Italy). D816V KIT mutation was detected on total RNA from mononuclear cell fractions of the BM samples.¹⁵ In the 2 patients who refused BM study, the D816V KIT mutation was searched for g-DNA from peripheral blood samples according to the method proposed by Kristensen et al.¹⁵ The diagnosis of SM was made according to current WHO guidelines.¹

RESULTS

Nineteen patients (2 females, age range, 41-83 years) were evaluated according to the aforementioned criteria (Table I). All of them had been previously diagnosed with HVA (6 *Polistes dominulus*, 12 *Vespa crabro*, and 1 honeybee) and have had a systemic reaction at first sting (grade IV according to Mueller in all but 1 case), most of them with loss of consciousness. All received a VIT course (range, 4-17 years), during which 13 patients were re-stung by the same causing insect and had only local reaction or large local reactions. One to 11 years after the VIT discontinuation, all patients had a field re-sting with a Mueller

TABLE I. Characteristics of the patients who were not protected after VIT discontinuation

Patient ID	Sex	Age (y)	Grade reaction at first sting	VIT	VIT duration (y)	Reaction at sting during VIT	Years to re-sting after VIT stopping	Reaction at re-sting
1	M	83	IV (lc)	<i>Vespula</i>	8	LR	5	IV (lc)
2	M	59	IV (lc)	Honeybee	5	LR	5	IV (lc)
3	M	51	IV (lc)	<i>Polistes</i>	5	LR	2	IV (lc)
4	M	39	IV (lc)	<i>Vespula</i>	4	Not stung	5	IV
5	M	76	IV	<i>Vespula</i>	10	LR	10	IV
6	M	52	IV (lc)	<i>Vespula</i>	5	Not stung	7	IV (lc)
7	F	50	IV (lc)	<i>Vespula</i>	4	LR	2	IV (lc)
8	M	50	IV (lc)	<i>Vespula</i>	6	LR	9	IV
9	M	41	IV (lc)	<i>Vespula</i>	4	Not stung	9	IV (lc)
10	M	55	IV (lc)	<i>Polistes</i>	4	LR	2	IV (lc)
11	M	55	IV (lc)	<i>Polistes</i>	5	LLR	9	II (U/A)
12	M	52	IV (lc)	<i>Vespula</i>	6	Not stung	11	IV (lc)
13	M	34	IV (lc)	<i>Polistes</i>	4	Not stung	1	IV
14	M	52	IV (lc)	<i>Vespula</i>	4	Not stung	10	IV (lc)
15	M	58	IV (lc)	<i>Polistes</i>	5	LLR	2	IV
16	M	66	IV (lc)	<i>Polistes</i>	4	LLR	1	IV (lc)
17	F	62	IV (lc)	<i>Vespula</i>	9	LLR	2	IV (lc)
18	M	60	IV (lc)	<i>Vespula</i>	17	LLR	9	IV (lc)
19	M	65	I	<i>Vespula</i>	10	LLR	4	IV

lc, Loss of consciousness; LLR, large local reaction; LR, local reaction; U/A, urticaria and/or angioedema.

TABLE II. BM study results of the 19 patients with severe reactions after VIT discontinuation

Patient ID	Major WHO criteria (yes/no)	c-KIT D816V mutation (yes/no)	MC CD25 positive (% of BM MNC)	MC CD2 positive (% of BM MNC)	>25% atypical BM MC (yes/no)	Serum tryptase level at re-sting (μg/L)	Skin involved (yes/no)*	Final diagnosis
1	Yes	Yes	0.6	0.6	Yes	22	No	BMM
2	No	Yes	0.016	0.015	No	13.1	No	MMAS
3	Yes	Yes	0.05	0.05	Yes	10.4	No	BMM
4	Yes	Yes	0.36	0.33	Yes	20.8	No	BMM
5	No	Yes	0.02	0.02	Yes	10.8	No	BMM
6	Yes	Yes	0.004	0.004	Yes	9.8	No	BMM
7	No	Yes	0.003	0.003	Yes	6.4	No	BMM
8	ND	Yes [†]	ND	ND	ND	8.4	Yes	MIS
9	Yes	Yes	0.02	0.02	Yes	15.7	No	BMM
10	No	Yes	0.034	0.034	Yes	22.3	No	BMM
11	No	Yes	0.01	0.01	Yes	26	No	BMM
12	Yes	Yes	0.011	0.011	Yes	11.2	No	BMM
13	No	Yes	0.03	0.03	Yes	13.6	No	BMM
14	ND	No [†]	ND	ND	ND	33.6	Yes	MIS
15	No	Yes	0.02	0.02	Yes	7.3	No	BMM
16	No	No	0.006	0.006	Yes	8.4	No	BMM
17	Yes	Yes	0.05	0.05	Yes	14.7	Yes	ISM
18	Yes	ND	0.1	0.1	Yes	13.3	No	BMM
19	No	No	0	0	No	20.3	No	nc-MCAS

BMM, Bone marrow mastocytosis; MMAS, monoclonal mast cell activation syndrome; MIS, mastocytosis in the skin; MNC, mononuclear cell; nc-MCAS, nonclonal mast cell activation syndrome; ND, not done.

*Confirmed by skin biopsy.

[†]Evaluated on peripheral blood sample.

IV grade reaction in all cases, but 1, with loss of consciousness. The calculated REMA score was 2 or more in 18 patients and the single case with a REMA score of less than 2 had an SBT of higher than 25 ng/mL, and thus all patients were evaluated for a possible CMD. The SBT level at the re-sting was less than 11.4 μg/L in 8 out of 19 patients (Table II).

At physical examination, 3 patients had limited skin lesions with positive Darier sign, confirmed as maculopapular CM at biopsy. These signs had not previously been reported by patients to their physicians. BM study was performed in all patients, with the exception of 2 patients with positive skin lesions who refused BM biopsy. In one of them the D816V kit mutation was

documented in peripheral blood. The results of the diagnostic assessment are presented in Table II. Final diagnoses were ISM with skin involvement ($n = 1$), BMM ($n = 14$), mastocytosis in the skin ($n = 2$), and monoclonal mast cell activation syndrome ($n = 1$), whereas a single patient did not show markers of clonality or atypical MC infiltration in BM and was classified as having nonclonal MC activation syndrome. Thus, a diagnosis of CMD was documented in 18 out of 19 (94.7%) patients who lost protection after VIT and had hypotension and/or elevated SBT. Of note, 8 out of 19 patients (42.1%) had normal SBT at the time of BM evaluation and all of them had a CMD (BMM in 7 cases and mastocytosis in the skin in 1 case).

DISCUSSION

The preferential association between HVA and CMD is now well recognized. This phenomenon was initially described in patients with CM¹⁶ and further confirmed in other case reports or series.¹⁶⁻²¹ Currently, it is well established that most adult patients with HVA and SM can be diagnosed even in the absence of skin lesions.²¹ Compared with other indolent forms (e.g., ISM), these patients are characterized by a male prevalence, a low occurrence of mediator-related symptoms, and a lower probability of having MC aggregates at BM examination.^{22,23} Moreover, they consistently have a KIT mutation restricted to MC only, whereas most patients with other subtypes of SM display KIT mutations also in the remaining myeloid lineages or lymphoid cells. The diagnosis of BMM remains a diagnostic challenge with important clinical and therapeutic implications. In cases with a clearly raised SBT level (>25 ng/mL), BM biopsy is usually recommended, whereas in patients with systemic HVA reactions and borderline or normal tryptase, the scoring system proposed by REMA (score) can be useful to decide whether patients should undergo BM biopsy.^{21,22} More recently, it was shown that the presence of hypotension may represent the most relevant factor to identify patients with HVA and mastocytosis, regardless of the baseline levels of tryptase.²³ Remarkably, a substantial part of our CMD cohort of patients ($n = 8$ [42%]) had normal levels of SBT at the re-sting after VIT completion and most of them ($n = 17$ [89.5%]) had hypotension without urticaria and/or angioedema after re-sting. Unfortunately, we cannot provide the pre-VIT SBT, because at that time the test was not routinely available, and at the end of VIT the test was not performed because the treatment had been effective, the subjects were symptom-free, and there was no suspicion of MC disorders. Probably, an assessment of SBT at the end of VIT could have provided useful information, but considering the available data and the rarity of the condition, we cannot recommend SBT assessment at the end of an effective VIT course as a routine approach.

CONCLUSIONS

VIT is recognized as a life-saving treatment for patients with HVA.²⁴ After some debate, mainly because of the safety concerns, it is now generally accepted that VIT is clinically justified in patients with severe HVA and documented mastocytosis. Several studies confirmed the effectiveness of immunotherapy in patients with mastocytosis with standard doses, even if in selected cases an increased dose could be required.^{25,26} A life-long VIT is now generally justified in these patients on the basis

of case reports of fatal anaphylaxis at re-sting after VIT discontinuation.²⁵⁻²⁸

However, some patients may remain excluded from this approach when mastocytosis is not recognized at the initial diagnosis of HVA. For this reason, we investigated a small group of patients who lost the protection by VIT after its discontinuation and had further episodes of systemic reactions. Of note, 95% of them, when deeply investigated by the most sensitive available techniques, had a CMD. The results obtained in such selected patients clearly documented that the probability of having mastocytosis (in any form) is quite high when VIT protection is lost after treatment. This would suggest that patients with HVA-induced anaphylaxis who lose protection after a proper course of VIT should be investigated for mastocytosis. Furthermore, when a diagnosis of mastocytosis is established, these patients should continue lifelong VIT.

REFERENCES

1. Horny HP, Metcalfe DD, Bennet JM, Bain BJ, Akin C, Escribano L, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: International Agency for Research on Cancer; 2008:54-63.
2. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391-405.
3. Sonneck K, Florian S, Müllauer L, Wimalaz F, Födinger M, Sperr WR, et al. Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: monoclonal mast cell activation syndrome. *Int Arch Allergy Immunol* 2007;142:158-64.
4. Alvarez-Twose I, González de Olano D, Sánchez-Muñoz L, Matito A, Esteban-López MI, Vega A, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *J Allergy Clin Immunol* 2010;125:1269-78.
5. Gonzalez de Olano D, de la Hoz Caballer B, Núñez López R, Sánchez Muñoz L, Cuevas Agustín M, Diéguez MC, et al. Prevalence of allergy and anaphylactic symptoms in 210 adult and pediatric patients with mastocytosis in Spain: a study of the Spanish network on mastocytosis (REMA). *Clin Exp Allergy* 2007;37:1547-55.
6. Bonadonna P, Zanotti R, Pagani M, Caruso B, Perbellini O, Colarossi S, et al. How much specific is the association between hymenoptera venom allergy and mastocytosis? *Allergy* 2009;64:1379-82.
7. Bonadonna P, Perbellini O, Passalacqua G, Caruso B, Colarossi S, Dal Fior D, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. *J Allergy Clin Immunol* 2009;123:680-6.
8. Zanotti R, Bonadonna P, Bonifacio M, Artuso A, Schena D, Rossini M, et al. Isolated bone marrow mastocytosis: an underestimated subvariant of indolent systemic mastocytosis. *Haematologica* 2011;96:482-4.
9. Pardanani A, Lim KH, Lasho TL, Finke CM, McClure RF, Li CY, et al. WHO subvariants of indolent mastocytosis: clinical details and prognostic evaluation in 159 consecutive adults. *Blood* 2010;115:150-1.
10. Biló BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN, EAACI Interest Group on Insect Venom Hypersensitivity. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005;60:1339-49.
11. Valent P, Escribano L, Broesby-Olsen S, Hartmann K, Grattam C, Brockow K, et al. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. *Allergy* 2014;69:1267-74.
12. Valent P, Akin C, Escribano L, Födinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37:435-53.
13. Perbellini O, Zamò A, Colarossi S, Zampieri F, Zoppi F, Bonadonna P, et al. Primary role of multiparametric flow cytometry in the diagnostic work-up of indolent clonal mast cell disorders. *Cytometry B Clin Cytom* 2011;80:362-8.
14. De Matteis G, Zanotti R, Colarossi S, De Benedittis C, Garcia-Montero A, Bonifacio M, et al. The impact of sensitive KIT D816V detection on recognition of indolent systemic mastocytosis. *Leuk Res* 2015;39:273-8.
15. Kristensen T, Vestergaard H, Bindsløv-Jensen C, Möller MB, Broesby-Olsen S, Mastocytosis Centre, Odense University Hospital. Sensitive KIT D816V

- mutation analysis of blood as a diagnostic test in mastocytosis. *Am J Hematol* 2014;89:493-8.
16. Ludolph-Hauser D, Ruëff F, Fries C, Schöpf P, Przybilla B. Constitutively raised serum concentrations of mast-cell tryptase and severe anaphylactic reactions to Hymenoptera stings. *Lancet* 2001;357:361-2.
17. Oude Elberink JNK, de Monchy JGR, Kors JW, van Doormaal JJ, Dubois AE. Fatal anaphylaxis after a yellow jacket sting, despite venom immunotherapy, in two patients with mastocytosis. *J Allergy Clin Immunol* 1997;99:153-4.
18. Rueff F, Placzek M, Przybilla B. Mastocytosis and Hymenoptera venom allergy. *Curr Opin Allergy Clin Immunol* 2006;6:284-8.
19. Alvarez-Twose I, Zanotti R, Gonzalez-de-Olano D, Bonadonna P, Vega A, Matito A, et al. Spanish Network on Mastocytosis (REMA); Italian Network on Mastocytosis (RIMA). Nonaggressive systemic mastocytosis (SM) without skin lesions associated with insect-induced anaphylaxis shows unique features versus other indolent SM. *J Allergy Clin Immunol* 2014;133:520-8.
20. Alvarez-Twose I, Bonadonna P, Matito A, Zanotti R, González-de-Olano D, Sánchez-Muñoz L, et al. Systemic mastocytosis as a risk factor for severe Hymenoptera sting-induced anaphylaxis. *J Allergy Clin Immunol* 2013;131:614-5.
21. Alvarez-Twose I, González-de-Olano D, Sánchez-Muñoz L, Matito A, Jara-Acevedo M, Teodosio C, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. *Int Arch Allergy Immunol* 2012;157:275-80.
22. Zanotti R, Lombardo C, Passalacqua G, Caimmi C, Bonifacio M, De Matteis G, et al. Clonal mast cell disorders in patients with severe Hymenoptera venom allergy and normal serum tryptase levels. *J Allergy Clin Immunol* 2015;136:135-9.
23. Bonadonna P, Zanotti R, Caruso B, Castellani L, Perbellini O, Colarossi S, et al. Allergen specific immunotherapy is safe and effective in patients with systemic mastocytosis and Hymenoptera allergy. *J Allergy Clin Immunol* 2008;121:256-7.
24. Gonzalez-de-Olano D, Alvarez-Twose I, Esteban-López MI, Sánchez-Muñoz L, de Durana MD, Vega A, et al. Safety and effectiveness of immunotherapy in patients with indolent systemic mastocytosis presenting with Hymenoptera venom anaphylaxis. *J Allergy Clin Immunol* 2008;121:519-26.
25. Niedoszytko M, De Monchy J, van Doormaal JJ, Jassem E, Oude Elberink JNG. Mastocytosis and insect venom allergy: diagnosis, safety and efficacy of venom immunotherapy. *Allergy* 2009;64:1237-45.
26. Bonadonna P, Zanotti R, Müller U. Mastocytosis and insect venom allergy. *Curr Opin Allergy Clin Immunol* 2010;10:347-53.
27. Reimers A, Muller U. Fatal outcome of a *Vespa* sting in a patient with mastocytosis after specific immunotherapy with honey bee venom. *Swiss Med Wkly* 2005;135(Suppl. 144):S14.
28. Wagner N, Fritze D, Przybilla B, Hagedorn M, Ruëff F. Fatal anaphylactic sting reaction in a patient with mastocytosis. *Int Arch Allergy Immunol* 2008;146:162-3.

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