



Mastocytosis as a risk factor for insect venom allergy

Patrizia Bonadonna · Elisa Boni · Roberta Zanotti

Received: 16 October 2019 / Accepted: 4 November 2019 / Published online: 2 March 2020
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Abstract

Background Clonal mast cell disorders (CMD) are characterised by the proliferation and accumulation of mast cells in bone marrow, skin and other tissues. The prevalence of CMD in patients with systemic hymenoptera venom allergy (HVA) is higher than in the general population.

Methods A review based on evidence from a thorough search in MEDLINE of the literature on CMD and its connection to HVA is presented.

Results Hymenoptera venom sting represents the most common trigger of anaphylaxis in adult mastocytosis patients and the anaphylactic reactions of patients with CMD and HVA are characterised by the absence of angioedema and erythema and the predominance of cardiovascular symptoms.

Conclusions Mastocytosis represents a risk factor for severe reaction in patients with HVA. An early diagnosis of CMD in these patients is very important since they are at high risk of severe osteoporosis and early therapy can be immediately started. Moreover, proper advice and prescription of adrenaline can be assessed.

Finally, in order to stop venom immunotherapy or whether to continue it lifelong, diagnosis of CMD has to be carried out.

Keywords Tryptase · Mast cell · Anaphylaxis · Mastocytosis · Insect venom allergy · Clonal mast cell disorders

Abbreviations

BM	Bone marrow
BMM	Bone marrow mastocytosis
CM	Cutaneous mastocytosis
CMD	Clonal mast cell disorders
HVA	Hymenoptera venom allergy
IgE	Immunoglobulins E
ISM	Indolent systemic mastocytosis
MC	Mast cell
MMAS	Monoclonal mast cell activation syndrome
MPCM	Maculopapular cutaneous mastocytosis
sBT	Serum basal tryptase
SM	Systemic mastocytosis
SSM	Smouldering systemic mastocytosis
WHO	World Health Organization

Introduction

Hymenoptera venom allergy (HVA) is a typical IgE-mediated disease, which clinical manifestations are the result of the mast cells (MCs) degranulation, triggered by the binding of the venom allergens to specific IgEs. Anaphylaxis is the most severe expression of these clinical manifestations, which is actually a severe and potentially fatal hypersensitivity reaction that can affect patients of all ages. It is the result of MC and basophil acute activation mediated by immunological or nonimmunological mechanisms, with consecutive massive release of vasoactive and proinflammatory substances from MCs, leading to

P. Bonadonna
 Allergy Unit, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

P. Bonadonna · R. Zanotti
 Multidisciplinary Outpatients Clinic for Mastocytosis (GISM), Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

Dr. E. Boni (✉)
 Allergy Unit, Hospital Santo Spirito, ASLAL, Via Giovanni Giolitti 2, 15033 Casale Monferrato, Alessandria, Italy
 boni6055@gmail.com

R. Zanotti
 Hematology Unit, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

the clinical signs and symptoms of anaphylaxis. In allergic reactions, degranulation of MCs develops in the first seconds after MC activation with binding of immunoglobulins E (IgEs) to the high affinity receptor FCεRI [1].

Risk factors for severe systemic anaphylactic reactions in hymenoptera venom allergic patients are the following: (i) history of prior sting reaction; (ii) high level of serum basal tryptase (sBT); (iii) vespid allergy; (iv) older age; (v) male sex; (v) ACE-inhibitor medication; (vi) mastocytosis [2].

Mastocytosis is a clonal mast cell disorder (CMD) which encompasses a heterogeneous group of clonal disorders characterised by the proliferation and accumulation of MCs and activation of pathological MCs in different tissues, with preferential localization in bone marrow (BM) and skin [3].

The great majority of cases are associated with somatic gain-of-function point mutations of *KIT*, a tyrosine kinase receptor (CD117) for the stem cell factor which is a growth factor for MCs. This mutation causes the receptor to be activated without the presence of a ligand, leading to proliferation of MCs. In adults with systemic mastocytosis (SM), the predominant mutation is at codon 816 in exon 17, where asparagine is substituted by valine (D816V) [4].

In a paediatric population with mastocytosis, it has been shown that the mutation D816V in exon 17 is detectable in only 35% of individuals, whereas in 40% mutations occur in exon 8, 9 or 11 and in another 25% no *KIT* mutation is detectable [5]. These relevant findings should be assessed in light of the most relevant features in children where mastocytosis is generally characterised by exclusive involvement of skin and resolves spontaneously in the majority of cases around puberty.

Clonal mast cells disorders

The prevalence of mastocytosis in European adult population is 0.96–1.3 per 10,000 inhabitants [6]. Subjects with mastocytosis can experience symptoms due to a massive MC activation and release of mediators. A multidisciplinary approach is essential since the clinical presentation of mastocytosis encompasses several symptoms: flushing, pruritus, urticaria, osteoporosis, diarrhoea, abdominal pain, anaphylaxis to several triggers and, in advanced variants of diseases, haematological alterations such as cytopenias and hepatosplenomegaly.

The diagnosis of systemic mastocytosis is based on World Health Organization (WHO) criteria (Table 1; [3]).

CMD includes cases not fulfilling sufficient criteria for SM but showing MC clonality markers by expression CD25/CD2 on immunophenotyping and/or *KIT* mutation at codon 816 on molecular analysis. These latter patients may have a limited, prediagnostic form of SM, also indicated as monoclonal mast cell activa-

tion syndrome (MMAS), but their risk of developing severe life-threatening anaphylaxis is similar to patients with SM [7–9].

In 2016 a revision of WHO classification was published (Table 2; [10]).

Cutaneous mastocytosis, defined as exclusive involvement of the skin is typical for children and represents about 5% of mastocytosis in adults. The most common presentations in children are maculopapular cutaneous mastocytosis (MPCM) in two variants (polymorphic and monomorphic) and cutaneous mastocytoma. The polymorphic variant of MPCM and mastocytoma in children are associated with more frequent spontaneous resolution. On the other hand, in adults, MPCM also known as urticaria pigmentosa is highly associated (90%) with SM [11].

Indolent systemic mastocytosis (ISM) is the most common form of mastocytosis (Fig. 1; [12]); a provisional subvariant without skin lesions (mastocytosis in the skin—MIS) is defined as bone marrow mastocytosis (BMM) [13, 14].

Patients with ISM have an excellent prognosis with normal or near-normal life expectancy [15, 16].

Smouldering systemic mastocytosis (SSM) is a new SM category in the WHO classification. The prognosis of patients with SSM is less favourable compared with ISM. The other forms, defined as advanced SM, are more rare and their survival is very unfavourable: this group includes aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasia, mast cell leukaemia and a rare localized aggressive variant, mast cell sarcoma.

Bone marrow mastocytosis

BMM is a subvariant of ISM defined by the absence of MIS [3]. Several studies reported a preferential association of anaphylaxis in adult patients with BMM than in ISM or cutaneous mastocytosis (CM) [8, 14, 17–20]. Likewise, among adult patients with mastocytosis (particularly in BMM patients), the most common trigger of anaphylaxis turned out to be hymenoptera venom [14, 19–22].

The Spanish and Italian groups focused attention on patients with BMM and HVA, highlighting peculiar clinical, biological and histologic features compared to those with BMM without HVA and ISM: male predominance, a distinct pattern of mediator-related symptoms, lower serum baseline tryptase, lower frequency of bone marrow multifocal, dense infiltrates (major diagnostic criterion for ISM) and absence of multilineage *KIT* mutation, which is considered the best indicator of good prognosis for ISM [16, 23]. Progression to aggressive variant of mastocytosis has not been yet reported in SM patients with HVA [24] and, on the contrary, HVA seems to be very rare in patients with aggressive subtypes of SM, who harbour the highest mast cell load [25, 26]. The majority of patients do not report MC activation symptoms between acute

Table 1 World Health Organization criteria for the diagnosis of systemic mastocytosis [3]

Major criteria		Minor criteria	
1.	Histological finding of at least 15 multifocal dense MC infiltrates in BM or other extracutaneous organs	1.	Abnormal morphology of extracutaneous MCs
		2.	Detection of a KIT mutation at codon 816 in extracutaneous organs
		3.	Expression of CD2 and/or CD25 on MCs in extracutaneous organs
		4.	Basal level of tryptase >20 ng/ml
Diagnosis of Systemic Mastocytosis: Major criterion + 1 Minor criterion or 3 Minor Criteria			
MC mast cell, BM bone marrow, KIT receptor of stem cell factor, CD2/25 cluster of differentiation and associated number			

Table 2 Classification of mastocytosis [10]

1.	Cutaneous Mastocytosis (CM)
2.	Systemic Mastocytosis (SM):
a.	Indolent Systemic Mastocytosis (ISM) – Bone Marrow Mastocytosis (BMM) (provisional variant)
b.	Smouldering Systemic Mastocytosis (SSM)
c.	Systemic Mastocytosis with an Associated Haematological Neoplasm (ISM-AHN, ASM-AHN, MCL-AHN ...)
d.	Aggressive Systemic Mastocytosis (ASM)
e.	Mast Cell Leukaemia (MCL)
3.	Mast Cell Sarcoma (MCS)

episodes; therefore, most of these patients may have severe HVA reactions as the unique clinical manifestations of mastocytosis [8, 27].

Clonal mast cell disorder and hymenoptera venom allergy

The literature confirms that there is a preferential association between HVA and mastocytosis [28] for several reasons:

- The prevalence of HVA in SM patients (20–30%) is higher than in the general population (0.3–8.9% in the European adult population) [29–31].
- Hymenoptera venom sting represents the most common trigger of anaphylaxis in adult mastocytosis patients (22–60% of cases) [12, 20–22]; on the contrary, in children with mastocytosis, hymenoptera stings play no role in eliciting anaphylaxis [21, 22].
- The association between HVA and mastocytosis is also confirmed by the higher prevalence of CMD in patients with systemic HVA (1–7.9%) than in the general population (1–1.3 cases per 10,000) [6, 32–36].

The anaphylactic reactions of patients with CMD and HVA are characterised in the majority of cases by the absence of angioedema and erythema and the predominance of cardiovascular symptoms, such as hypotension leading to loss of consciousness [23, 37].

Allergological workup in HVA includes skin test aimed to establish venom to be used for immunotherapy. Skin tests with venoms are generally safe, even in patients with mastocytosis [38, 39] even when tests are carried out simultaneously at different concentra-

tions, but a preliminary step has been recommended. Only after reading the reactions to this first set, should a higher concentration be used. This caution is to be especially maintained in patients with a history of severe anaphylactic reaction or suffering from mast cell disorders [40].

In a recent study, Brockow et al. analysed in SM patients, sIgE reactivity for yellow jacket and honeybee venom allergens with the recombinant technique and the author showed that even if there are no obvious differences in the reactivity profiles of hymenoptera venom-allergic patients with and without mastocytosis, a large portion of patients with mastocytosis had sIgE levels against the allergenic components in the range between 0.1 and 0.35 kUA/l. Therefore, the authors concluded that a diagnostic cut-off of 0.1 kUA/l and a combination of the major allergens Ves v 1 and Ves v 5 should be applied [41].

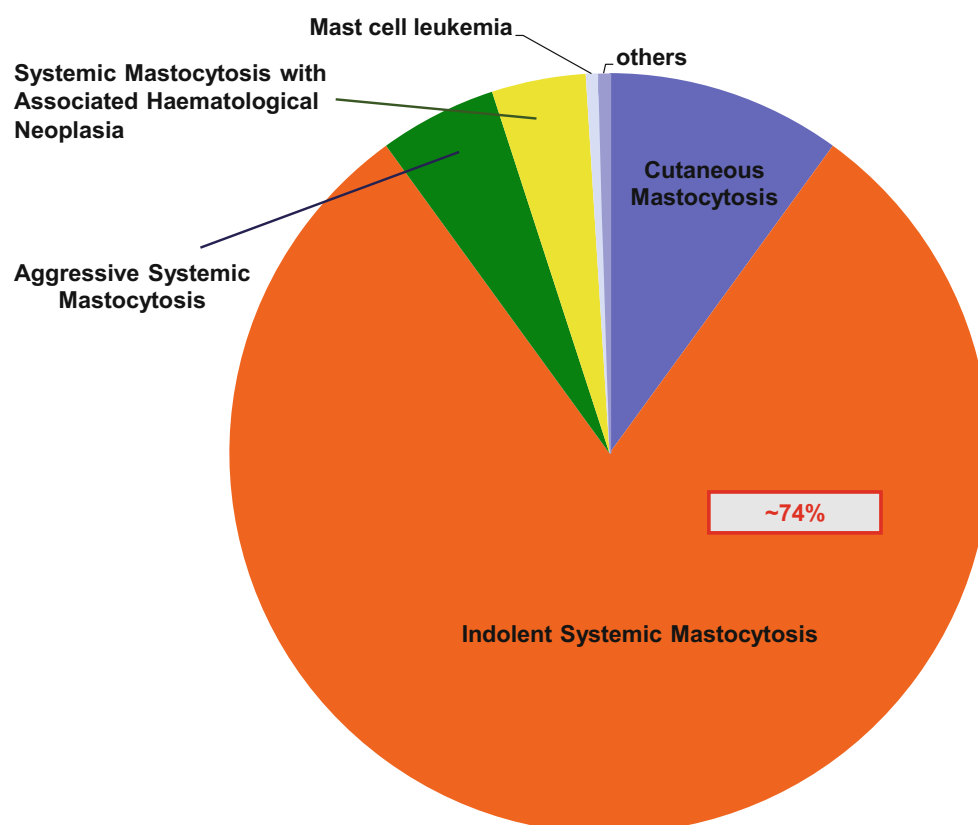
Identification of hymenoptera venom allergic patients who need the haematological workup for systemic mastocytosis

Association between HVA and mastocytosis is strong. Three possible scenarios all worthy of further haematological study can occur.

1. Patients with severe reaction to hymenoptera sting with high level of tryptase with or without MIS

In a previous study, our group showed that subjects with a history of severe systemic reactions to hymenoptera stings and increased sBT level (>11.4 ng/mL) undergoing an haematological workup, which included not only BM biopsy and aspiration but also

Fig. 1 Rate of clinical presentations of mastocytosis [12]



flow cytometric analysis and KIT mutation detection, were diagnosed in 88.2% as having CMD. Out of these subjects with CMD, 21 subjects (61.7%) have ISM, in which 14 fulfilled both major and minor criteria and 7 satisfied three minor criteria and 9 subjects (26.5%) have MMAS. Therefore 47% of diagnoses of ISM/MMAS have been diagnosed thanks to flow cytometry, KIT mutation analysis, or both, which increase the sensitivity of the haematological workup [9].

2. Patients who have HVA presenting with hypotension and loss of consciousness without urticaria and angioedema during the anaphylactic reaction even in case of normal serum tryptase

Hypotension in the absence of urticarial/angioedema may represent the most relevant factor to identify those patients with HVA and CMD regardless of the sBT levels. sBT values ≥ 7.95 ng/mL seems to be associated to the risk of SM with the highest values of sensitivity and specificity in case of severe anaphylaxis without skin symptoms [37].

Our group studied a selective group of 22 patients with history of one or more episodes of anaphylaxis with documented hypotension and/or loss of consciousness with absence of urticaria and angioedema and without MIS and with sBT below of 11.4 ng/mL. The diagnosis of CMD was made in 16/22: 15 cases of ISM and 1 case of MMAS. In all cases of ISM the diagnosis was based only on minor criteria, since the

major criterion was not present at BM biopsy [37]. Therefore, BM study should be necessarily performed in reference centres for MC diseases, using highly sensitive and adequate techniques.

For the analysis of MC immunophenotype, a high sensitive multiparameter flow-cytometry approach is essential. A combination of five monoclonal antibodies (CD45, CD117, CD34, CD25, and CD2) and the acquisition of at least 1–3 million events should be applied to avoid a risk of a false negative test [42].

Our results are in agreement with the REMA score, proposed by the Spanish group and based on gender, clinical characteristics of anaphylaxis and sBT (Table 3). In patients suffering from systemic MC activation symptoms—mainly HVA—and without MIS, it is able to predict MCD with a high sensitivity and specificity [8, 43]. This score could be easily applied by general practitioners and medical specialists in order to avoid unnecessary BM studies.

3. Patients with severe reaction to hymenoptera sting and negative skin and serological test for HVA

In several studies, the authors suggest that there is an association between hymenoptera anaphylaxis with a negative allergy study and the presence of an underlying SM. This phenomenon has been attributed to an increased absorption of circulating IgE by large amounts of mast cells and to direct mediator release from tissue MCs induced by venom components [9,

Table 3 The REMA Score (Red Española de Mastocitosis) [43]. Proposed as a screening method for the presence of clonal mast cells in patients presenting with anaphylaxis in the absence of cutaneous mastocytosis before a bone marrow study. BM study should be performed in all cases with REMA score ≥ 2

Variable		Score
Gender	Male	+1
	Female	-1
Clinical symptoms	Absence of urticaria, pruritus and angioedema	+1
	Urticaria, pruritus and/or angioedema	-2
	Presyncope and/or syncope	+3
Basal tryptase	<15 ng/mL	-1
	>25 ng/mL	+2

38, 44]. Due to very limited number of reported cases further studies are needed to confirm this close association.

Conclusions

Early diagnosis of CMD in patients with severe HVA represents a substantial advantage for several reasons. Patients with CMD are at high risk of severe osteoporosis and early therapy can be immediately started to prevent vertebral fracture. Furthermore, proper advice and prescription of adrenaline (two autoinjectors) can be assessed. Finally, in order to stop venom immunotherapy or whether to continue it lifelong, diagnosis of CMD has to be carried out [45].

Acknowledgement This work was partially presented as a lecture in the EAACI Allergy School on Insect Venom Allergy and Mastocytosis held in Groningen, The Netherlands, April 11–13, 2019.

Author Contribution All authors performed the literature search and data analysis and revised the work.

Conflict of interest P. Bonadonna, E. Boni and R. Zanotti declare that they have no competing interests.

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