

Mast Cell Activation Syndromes and Environmental Exposures

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Published online: 20 January 2018

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This article is part of the Topical Collection on *Occupational Allergy*

Keywords Clonal · Environmental · Mast cell · Mast cell activation syndrome · Mastocytosis · Occupational

Opinion statement

Mast cell activation syndromes (MCAS) are an emerging entity that includes a heterogeneous group of diseases presenting with typical signs and symptoms secondary to the release of mast cell (MC) mediators. Triggering factors underlying the activation of mast cells show a wide variability, and episodes of MC-mediator release are usually triggered by idiopathic or by mixed causes, which makes avoidance recommendations difficult to devise. Sometimes, environmental or occupational exposures are responsible for MC activation. In this article, we review the main workplace environment eliciting factors described in MCAS and the current guidance on treatment.

Introduction

The term mast cell activation syndrome (MCAS) has recently emerged and encompasses a heterogeneous group of diseases characterized by signs and symptoms derived from mast cell (MC) activation [1, 2]. MCs are immune system effector cells that originate from a hematopoietic precursor cell. They are preferentially found in connective tissue and are more numerous in areas that may come into contact with antigens, such as the dermis,

areas in the proximity of blood vessels, lymphatic vessels and nerves [3], the mucosa and submucosa of the digestive tract [4], the conjunctiva [5, 6], and the alveoli and the airways [7]. In allergic reactions, MC activation is caused by immunoglobulin E (IgE)-specific antibodies in response to an antigen, but MCs can also be triggered by other non-IgE mediated immunological mechanisms and by non-immunological mechanisms, such as

biological or environmental substances, complement activation products, cytokines, chemical agents, occupational triggers, and physical stimuli [8]. Many of these activation factors can be present in the workplace,

potentially affecting workers suffering from MCAS. Herein, we review the current classification of MCAS, the main triggers of MC mediator release in MCAS—including environmental ones—and the suggested management.

Mast cell disorders: definition, classification, clinical features, and diagnosis

Mastocytosis

Mastocytosis (SM) is a miscellaneous group of uncommon diseases characterized by the presence of abnormal MCs in various organs and systems [9, 10]. Two relevant findings have been described with regard to the pathogenesis of this disease: activating somatic mutations in the *KIT* molecule (mostly the Asp816Val-D816V-*KIT* mutation) and the existence of an aberrant immunophenotype in the expression of CD25 by MCs. The World Health Organization (WHO) currently recognizes seven categories of SM [9]. The diagnosis of SM is based on the concurrence of one major criterion and one minor criterion or ≥ 3 minor criteria in the absence of the major criterion. The major criterion is the demonstration of multifocal aggregates of ≥ 15 MCs in bone marrow (BM) sections or in other extra-cutaneous tissues. Minor criteria include the following: (i) identification of $> 25\%$ of morphologically abnormal MCs in BM smears, (ii) demonstration of an aberrant expression of CD25 and/or CD2 on MCs, (iii) detection of the activating mutations in codon 816 of the *KIT* gene, and (iv) presence of serum baseline tryptase (sBT) levels $\geq 20 \mu\text{g/L}$ [9].

The most frequent subtype of SM ($\sim 80\%$ of all SM cases) is indolent systemic SM (ISM) [11] and may present with (ISMs+) or without (ISMs-) skin lesions (80 vs. 20% approx., respectively) [12]. This subtype, specially ISMs-, is frequently undersuspected due to the lack of specificity of presenting clinical symptoms that can overlap with those found in more common allergic diseases. Its final diagnosis is also challenging since MCs represent a very small proportion of all nucleated BM cells (usually fewer than 10^{-3} BM MCs [13], BM MC aggregates are frequently not found in such patients (in around 30% of cases), and serum baseline tryptase levels are usually under $20 \mu\text{g/L}$).

Mast cell activation syndromes

MCASs include all the patients who fulfill the proposed criteria [1]: (i) typical signs and symptoms secondary to the release of MC mediators, affecting at least two organs, together with (ii) objective evidence of mediator release (elevation of sBT, histamine metabolites of prostaglandins in 24-h urine), and (iii) response to anti-mediator treatment. The current classification of MCAS, based on a consensus proposal, differences three categories [1, 2]: (i) primary, (ii) secondary, and (iii) idiopathic MCAS (see Table 1). According to the Spanish Network on Mastocytosis (REMA), the cornerstone of MCAS classification should be the presence (or absence) of clonal MCs, as defined by the expression

Table 1. Summary of MCAS classification

Current classification [1, 2]	REMA proposal [14•]
Primary ^a	
-Mastocytosis	
-Monoclonal mast cell activation syndromes (MMAS)	Clonal MCAS
Secondary	
-Allergic disorders	
-Mast cell activation associated with chronic inflammatory or neoplastic disorders	
-Physical urticarias	
-Chronic autoimmune urticaria	Non-clonal MCAS
Idiopathic	
-Anaphylaxis	
-Angioedema	
-Urticaria	
-Mast cell activation syndrome (MCAS)	
^a Defined by the expression of CD 25 or <i>KIT</i> mutation, or both	

of CD 25 or *KIT* mutation, or both. All other patients with clinical signs of release, without cutaneous lesions and without clonal MCs, are considered to have non-clonal MCAS (nc-MCAS) [14•].

Clinical features

Clinical symptoms upon MC activation may vary from pruritus, flushing, or gastrointestinal symptoms to syncopal or near-syncopal episodes. Clinical presentation of ISMs + patients might be heterogeneous, unlike ISMs- and clonal-MCAS, which are frequently associated with the presence of anaphylaxis with cardiovascular collapse symptoms, in the absence of urticaria and angioedema [15••,16].

Diagnosis

Diagnosis of SM is often delayed because many physicians are unfamiliar with this illness. This can lead to substantial morbidity and puts patients at risk of complications. The final diagnosis of MC diseases requires a bone marrow biopsy study using highly sensitive and specific methodological techniques, including cytology [17], histology and immunochemistry [18, 19], flow cytometry immunophenotyping [20–22], and the study of *KIT* mutation in purified MCs [23, 24]. This is especially relevant in ISMs- and c-MCAS, where BM MCs are present at low frequencies. All these techniques are usually not widely available, and thus, patients with a suspicion of MC disorders (MCD) should be studied in specialized reference centers. The REMA has proposed a highly sensitive and specific predictive model (REMA

score) to help screen for clonality in patients with MCAS in the absence of skin lesions [15••, 25]. The European Competence Network on Mastocytosis recommends using the REMA score to predict the presence of clonal MCs prior to a BM study [26].

Triggers of mast cell activation

Triggering factors underlying MC activation in patients with systemic SM may present with a wide interindividual variability [27, 28]. Such variation mainly responds to idiosyncratic factors but also to concurrent specific sensitizations and geographic considerations [28]. Furthermore, as specific triggers have been associated to specific subtypes of SM (particularly hymenoptera stings to ISMs- and c-MCAS [29]), avoidance should be individualized. It has also been observed that in patients having >5 episodes of MC-mediator release, these episodes are mainly idiopathic or triggered by mixed causes [15••]. Consequently, the identification of a possible trigger is of vital relevance as strict avoidance of the trigger is an essential part of treatment. However, unpredictability is one of the most important aspects of impairment in quality of life in patients with MC disorders [30]. Children with MCD, despite its often transient nature, may also experience challenging disease-associated symptoms due to spontaneous or trigger-induced MC degranulation [31]. Table 2 shows the most relevant factors that can induce the release of MC mediators in SM and their frequency. Nevertheless, triggering agents are frequently difficult to identify. Most studies are performed with surveys, in which patients find it difficult to differentiate between allergy, intolerance, triggers, and provoking factors [30].

Table 2. Triggers of mast cell mediator release in MCAS

Environmental	Non-environmental
Frequent	Frequent
-Bee and wasp venoms	-Idiopathic
-Heat/cold, changes in temperature	-NSAIDs and opioids
	-Physical agents as friction of skin lesions and fever.
Rare	Rare
-Other venoms: mosquito, fire ant, <i>hippobosca equine</i> , snake	-Other drugs: anesthetics, contrast media, interferon, vaccines, dextrans
-Aeroallergens ^a	-Foods
-Chemicals inhalation	-Exercise
	-Emotional factors
	-Miscellaneous: alcohol, menstruation, pain, teething (children).

Adapted from [28]

NSAIDs nonsteroidal anti-inflammatory drugs

^aCommon inhalants such as pollen, house dust mites, molds, and danders

Allergens in environmental exposures

Although a great instability of factors has been described as MC activating elicitors, any workplace environmental allergen might theoretically cause a severe systemic reaction in an allergic worker with SM, even in a previously indolent disease [32••]. The main environmental allergens reported in MCD are described below.

Insects

Insects, particularly wasp and bee stings, have been described as the most common elicitors of anaphylaxis in patients with SM [16, 29, 33••]. In fact, specific immunological disorders such as SM constitute a well-known risk factor for fatal venom anaphylaxis [34]. The prevalence of clonal MCAS in subjects with hymenoptera venom anaphylaxis (HVA) ranges from 1 to 7.9% [35], while the prevalence of HVA in patients with any form of SM is higher than 20% [29, 36–38]. In fact, evidence of an association between hymenoptera venom allergy and SM has been highlighted by the prevalence of HVA among patients with SM, which varies between 23 and 47% [35, 37–40]. The hymenoptera order includes wasp, ants, bees, and flies. The professionals most frequently affected by occupational venom allergy are beekeepers, but other outdoor workers such as gardeners, farmers, truck drivers, masons, and forestry workers [41] present a 100- to 1000-fold increased risk compared to the general population [42]. Diagnosis of these disorders should be a priority in sensitized workers exposed to wasps, bees, as well as wood ants and fire ants [43], since treatment and recommendations might differ from general population patients. Unfortunately, it has been reported that only 66% of beekeepers who attend any emergency unit for systemic reactions are later evaluated by an allergist [44]. Proper prevention and management strategies in the workplace are mandatory and should include the presence of on-site injectable adrenaline and the possibility of prescribing a highly effective treatment such as subcutaneous venom immunotherapy, which is cost-effective in those specific high-risk groups with frequent stings and reactions [45].

Otherwise, the type of insect eliciting reactions in outdoor workers might differ from those in the non-occupational setting. As an example, white-faced hornets are considered beneficial due to their predation of flies, caterpillars, and spiders. However, their aggressively defensive nature makes them a threat to workers who wander too close to a nest or when a nest is too close to human habitations, and white-faced hornet stings have been described as potential inducers of anaphylactic reaction in subjects with elevated and asymptomatic serum tryptase [46]. Bumblebees are increasingly used for pollination of greenhouse plants such as tomatoes, zucchini, and peppers, but this rise in their use has also led to an increase in the frequency of adverse reactions to bumblebee venom in greenhouse workers [47].

Other insects could elicit systemic reactions in workers suffering from systemic SM. Mosquito bites have been associated to anaphylaxis in a case report [48]. The case of a male pine-resin worker who developed anaphylaxis with loss of consciousness and sphincter relaxation 10 min after direct skin contact with a pine processionary caterpillar has also been reported [49•]. In this case, the diagnosis of SM was confirmed by the presence of high serum baseline tryptase, histologic findings in bone marrow, and molecular analysis of the D816V *KIT* mutation,

confirming the presence of specific IgE to *Thaumatococcus pinnatifidus*. Among the arthropods, *Chironomidae* larvae and *Gammarus* species have been implicated in anaphylaxis in aquarists who use them as fish food [50]. Tick bites can also trigger specific IgE reactions that could affect shepherds, maintenance workers, farmers, or gardeners [32••]. Finally, other professions like herpetologists could also be at risk of systemic reactions caused by handling of venom or snakebites [41].

Aeroallergens

A web-based survey performed among 420 US patients with MC disorders showed that more than half (58.1%) reported allergic symptoms to environmental substances and/or inhalants [30]. This percentage is similar to the one reported in another series where 93 of 163 (57%) Spanish patients with SM reported allergic symptoms, although the prevalence of allergy symptoms attributable to an IgE sensitization in this population was 23.9% [37]. This supports previous reports stating that the prevalence of allergy among patients with MC disorders is similar to that of the general population [38]. The aeroallergens responsible for sensitization were pollen, dander, dust mites, and molds, prompting mostly nasal and ocular symptoms [37].

Changes in temperature

There is a close association between changes in temperature, especially hot temperature, and MC activation-related symptoms [28]. In a clinical survey of the American mastocytosis society (TMS), 82.2% of patients reported heat as a trigger of MC-degranulation [30]. Other physical stimuli, such as hydrostatic pressure or friction of skin lesions, have also been reported as potential triggers [51] and have been associated with aggravation of the skin reactions [52], but are unlikely to be considered as environmental triggers.

Chemical substances

Odors (47.5%) and chemicals (4.9%) are among the triggers listed as eliciting factors of symptomatology in the questionnaire carried out by TMS, mostly among women with non-clonal MCAS [30]. Perfume inhalation has also been described as a trigger involved in acute MC-mediator release episodes in patients with MCD [16].

Other environmental exposures

In a recent study analyzing a cohort of adult patients diagnosed with SM [52], the rate of allergen sensitization was significantly higher in SM patients with anaphylaxis (43%) than in non-anaphylaxis SM patients, 70 vs. 23%, respectively ($p = 0.0002$). Interestingly, 13/32 patients with SM and anaphylactic reaction were sensitized to animal dander, as compared to only one of the patients who had never experienced anaphylaxis. This observational finding might be relevant if we consider that workers exposed to laboratory animals may suffer from severe allergic reactions to animal bites, particularly from rodents or horses, when sensitized workers are exposed to large quantities of animal allergens in the saliva [41]. Some allergens described as frequent

inducers of occupational anaphylaxis such as latex, foods, or drugs affect employees in their manufacturing process and could theoretically be involved in severe reactions in workers with SM, but to the best of our knowledge, no other cases have been reported at this time.

Treatment of MCAS

General treatment

There is currently no cure for MCAS, and its treatment is limited to the following: i) counseling and training of the patients, relatives, and their physicians in the management of the disease; (ii) avoidance of triggers; and (iii) control of the symptoms due to the release of MC according to symptom severity with conventional anti-mediator treatment such as histamine receptor blockers, sodium cromolyn, leukotriene antagonists, corticosteroids, and epinephrine [28, 29]. In refractory cases, treatment with the anti-IgE Omalizumab has also been reported to be occasionally useful [53].

Specific treatment for environmental exposures

Insects

Venom immunotherapy (VIT) in MCAS, as in the general population, is only recommended for patients with IgE-mediated sensitization (bee or wasp) as demonstrated by positive skin tests and/or by in vitro specific IgE [12, 54–56]. VIT is effective to treat IgE-mediated hymenoptera venom anaphylaxis (HVA) in these patients, and its use is recommended despite a relatively high risk of adverse reactions during the build-up phase since it provides protection [12, 57, 58]. The question which still needs to be answered is how long should the standard duration (3 to 5 years) of VIT be in these patients with a greater MC burden and a known risk of presenting a higher frequency of HVA [12].

While workers sensitized to bumblebee venom have primary sensitization to bumblebee venom, non-workers seem to present prior bee venom sensitization and a cross-reactivity pattern. Because allergic workers show scarce cross-reactivity with bee venom, the European Academy of Allergy and Clinical Immunology recommends the use of specific bumblebee venom for immunotherapy [59].

Aeroallergens

Like VIT in patients with HVA, specific immunotherapy against common aeroallergens (pollen, dust mites, molds, and animal dander) is also effective and safe and should be prescribed when an IgE-mediated allergy is demonstrated. Skin testing can be done safely in patients with systemic SM and other MCD [37].

Changes in temperature

Patients with SM should avoid drastic changes in temperature. The main recommendations are the use of air conditioning when necessary and of mildly warm water for bath/shower [28].

Chemical substances

As previously described with other triggers, the avoidance of fragrances, odors, and any other chemical substance is recommended in MCD patients.

Conclusions

MCASs, despite being uncommon diseases, can be associated with severe reactions, including anaphylaxis. An accurate diagnosis is mandatory in order to prevent occupational exposures capable of eliciting severe reactions. Professionals attending workers at risk should improve their knowledge in this group of diseases to early identify MCAS patients, so as to be able to provide them with the right prevention measures.

Acknowledgements

We thank Isabel Coman for her technical assistance with the revision of the English version of the manuscript.

Funding

This work was supported by a grant from the Sociedad Española Alergia e Inmunología Clínica 2014.

Compliance with ethical standards

Conflict of interest

David González-de-Olano declares that he has no conflict of interest. Javier Domínguez-Ortega declares that he has no conflict of interest. Silvia Sánchez-García declares that she has no conflict 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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