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Anaphylaxis as a Clinical Manifestation of Clonal Mast Cell Disorders

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Abstract Clonal mast cell disorders comprise a heterogeneous group of disorders characterized by the presence of gain of function *KIT* mutations and a constitutively altered activation-associated mast cell immunophenotype frequently associated with clinical manifestations related to the release of mast cells mediators. These disorders do not always fulfil the World Health Organization (WHO)-proposed criteria for mastocytosis, particularly when low-sensitive diagnostic approaches are performed. Anaphylaxis is a frequent presentation of clonal mast cell disorders, particularly in mastocytosis patients without typical skin lesions. The presence of cardiovascular symptoms, e.g., hypotension, occurring after a hymenoptera sting or spontaneously in the absence of cutaneous manifestations such as urticaria is characteristic and differs from the presentation of anaphylaxis in the general population without mastocytosis.

Keywords Anaphylaxis · Clonal mast cell disorders · Indolent systemic mastocytosis in the absence of skin lesion · *KIT* mutation

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Abbreviations

AAAAI	American Academy of Allergy Asthma and Immunology
ACAAI	American College of Allergy Asthma and Immunology
ASM	Aggressive systemic mastocytosis
BM	Bone marrow
BM MC	Bone marrow mast cells
c-MCD	Clonal mast cell disorders
c-MACD	Clonal mast cell activation disorders
CM	Cutaneous mastocytosis
ISM	Indolent systemic mastocytosis
$ISMs^-$	Indolent systemic mastocytosis in the absence of skin lesions
$ISMs^+$	Indolent systemic mastocytosis with skin lesions
MC	Mast cells
MCAS	Mast cell activation syndrome
MCL	Mast cell leukemia
MH	Methylhistamine
MIMA	Methylimidazole acetic acid
MMAS	Monoclonal mast cell activation syndrome
NSAIDs	Nonsteroidal antiinflamatoy drugs
REMA	Spanish Network on Mastocytosis
sBT	Serum baseline tryptase
SM	Systemic mastocytosis
VIT	Venom immunotherapy
WAO	World Allergy Organization
WDSM	Well-differentiated systemic mastocytosis
WHO	World Health Organization

Introduction

Anaphylaxis is defined as "a serious, life-threatening generalized or systemic hypersensitivity reaction" and "a serious

allergic reaction that is rapid in onset and might cause death" [1–3]. The true global rate of anaphylaxis for all triggers in the general population remains unknown, due to several factors including underrecognition, underdiagnosis, underreporting, and the usage of different reporting measures, e.g., incidence vs. prevalence [4••]. Despite this, population-based studies estimate that the incidence rate of anaphylaxis in the USA and Europe would range from 1.5 to 50 cases per 100,000 person-years [5, 6], whereas lifetime prevalence is estimated to be of 0.05–2 %, seemingly increasing in recent years [5–9]. Furthermore, a higher incidence rate of anaphylaxis of 103 episodes per 100,000 person-years was recently reported in the Spanish population; interestingly, a peak of 314 episodes per 100,000 person-years was observed in early (0–4 years) childhood [10]. Similarly, emergency and critical care admissions due to anaphylaxis in the UK are also increasing, representing 0.1 and 0.3 % of all pediatric and adult admissions in 2009, respectively [11].

Factors that are associated with an increased risk for severe or fatal outcomes [4••, 12] include the presence of a clonal mast cell disorder (c-MCD) [13, 14] including mastocytosis [15–17].

Diagnostic Criteria for Anaphylaxis

Following the World Allergy Organization (WAO) criteria [4••], the diagnosis of anaphylaxis is primarily based on clinical findings obtained through a detailed anamnesis and the recognition of the symptoms and signs present minutes to few hours after exposure to a known (or most likely) allergen or trigger for the patient. Typically, symptoms occur in ≥2 body systems mostly including skin and mucosal, the upper and lower respiratory tract, the gastrointestinal tract, the cardiovascular system, and/or the central nervous system. Therefore, anaphylaxis can present with skin and/or mucosal tissue involvement plus respiratory manifestations, gastrointestinal symptoms, reduced blood pressure, or even signs or symptoms of end-organ dysfunction. Usually a combination of two or more of these clinical manifestations are observed, although in some circumstances, anaphylaxis is also diagnosed when only one body system is clinically involved, e.g., reduced blood pressure observed few minutes to several hours after exposure to a trigger for the patient and generalized urticaria with a sudden onset after allergen immunotherapy as the only initial manifestation [2, 18]. Skin involvement is the most frequent sign of anaphylaxis (around 80–90 % of cases), which may lead to delayed diagnosis in patients presenting with other than skin signs. In c-MCD including mastocytosis, anaphylaxis presenting with hypotension without skin signs and/or exposure to a known trigger is frequently observed [19].

Laboratory Tests in Anaphylaxis

The determination of different mast cells (MC) mediators, such as serum and/or plasma histamine and tryptase, is proposed for the diagnosis of anaphylaxis [4••, 20]. Optimal blood sampling for measurement of histamine and tryptase levels should be performed 15–60 and 30–180 min after the onset of the symptoms, respectively. However, results from these tests may not be available in an emergency setting [3, 21] and may not be specific for anaphylaxis.

Histamine and tryptase are both produced and accumulated in tissue MC and blood basophils (i.e., tryptase is accumulated in smaller quantities in basophiles vs. MC) [22]. Tryptase includes a group of several proteases, and there are two predominant forms α- and β-tryptase, but also δ-tryptase and γ-tryptase; all of them are coded by genes localized on chromosome 16 [23, 24]. α-Protryptase is released constitutively from MC into the plasma [25], while a specific release of β-tryptase during anaphylaxis has been reported [26]. The commercial available assay (ImmunoCAP Tryptase, Thermo Fisher Scientific) detects α-pro- and β-tryptases (total tryptase). Increased total serum baseline tryptase (sBT) levels have been reported in other conditions different from anaphylaxis such as systemic mastocytosis (SM) [25, 27], myeloid malignancies [28], a subset of hypereosinophilic syndromes [29], chronic urticaria [30], and patients with decreased renal function [31, 32]. While increased serum tryptase levels are often present in anaphylaxis evoked by insect stings, injected drugs, or in the presence of cardiovascular symptoms (e.g., hypotension) during the episode, all of which are associated with a high suspicion for an underlying c-MCD [27, 33, 34], normal serum tryptase levels are often found in anaphylaxis triggered by foods and anaphylaxis in the absence of reduced blood pressure [35]. In food-induced anaphylaxis, MC degranulation seems to be restricted to the gut;[36] furthermore, mucosal MC contain less tryptase than skin MC [37], whereas both types of tissue MC have similar levels of histamine, supporting the notion that increased histamine levels could be more useful than tryptase in food-induced anaphylaxis [20]. Monitoring of tryptase levels during an anaphylactic episode followed by sBT determination after recovery is more informative than an isolated determination. In this regard, in a prospective study in adults in which sBT concentrations were measured sequentially 1–2, 4–6, and 12–24 h after the onset of anaphylaxis and later on at baseline, it was shown that 62 % of the patients initially had elevated tryptase levels (mean of 19.3 ±15.4 μg/L), a positive correlation being observed between the grades of severity of anaphylaxis and serum tryptase levels ($p<0.001$, $r=0.49$); of note, two cases diagnosed of mastocytosis were excluded from the analysis, although mast cell clonality was not ruled out in the remaining cases [38].

Elevated histamine plasma levels have been reported in 92 % of cases in a series of 65 patients who presented

perianesthetic anaphylaxis, in whom the coexistence of an underlying c-MCD was not ruled out [39]. This is relevant because SM patients frequently show increased levels of urinary histamine metabolites such as methylimidazole acetic acid (MIMA) and methylhistamine (MH) [40]. The identification of normal histamine levels, as also described above for tryptase, does not rule out the diagnosis of anaphylaxis [35]. Other blood tests for serum/plasma β-tryptase, platelet activating factor (PAF)—recently related to the severity of the acute allergic reaction [41]—and carboxypeptidase A3, as well as 24-h urinary prostaglandins (prostaglandin D2; 11 platelet-derived growth factor 2) and cysteinyl leukotrienes (LTE4) [42–45], are not available in a routine clinical basis and should always be compared with the patient's baseline values. Of note, enhanced levels of cysteinyl leukotrienes, (LTB4, LTC4, LTD4 and LTE4) [46, 47] in association with significant upregulation of genes involved in lipid metabolism, probably leading to an increased production of arachidonic acid metabolites (eg, prostaglandin D2 and leukotriene C4) [48] have also been described in mastocytosis.

Specific biomarkers of anaphylaxis are lacking at the present time, but measurement of tryptase and/or histamine levels as well as other mediators may be highly informative in specific subsets of patients [4••].

Characterization of Clonal Mast Cells

Mast cells are a key structural and functional component of the immune system; they play a key role in inflammatory reactions in allergic and nonallergic processes [49–53]. Activation through cross-linking of high-affinity Fc receptors for IgE (FcεRI) on the cytoplasmic membrane of normal and reactive MCs elicits the release of inflammatory mediators from MC secretory granules in IgE-sensitized MC resulting in a critical step in immediate hypersensitivity reactions [50, 51]. The release of MC mediators can be also elicited through Fcγ (gamma) [54–56], by aggregated IgG or through C3a [57]. Normal and reactive MC also express on their cell surface toll-like receptors (TLR) 4 and TLR2, CD48, and other complement receptors [49, 52, 58–61] which can activate MC in the absence of a specific antibody or other immunological signaling [62].

Normal and reactive MC as well as clonal MC from patients with SM or c-MCD express a number of functionally relevant cell surface antigens related to MC activation like the stem cell factor receptor (c-kit or CD117), high-affinity receptors for IgE (FcεRI), IgG (FcγR), LAMP molecules such as CD63, and complement-related receptors and regulatory molecules, among other proteins.

Gain-of-function point mutations involving the tyrosine kinase domain of *KIT,* most frequently involving the D816V single change in the exon 17 of *KIT*, are present in MC from the most adult SM (>90 %) in association with an aberrant CD25+ immunophenotype [63]. The D816V mutation as well as other much less frequent "enzymatic pocket" type *KIT* mutations found in SM patients (e.g., other *KIT* mutations involving codons 815, 816, 817, 820, and 839) [64] directly affects the enzymatic site at the TK2 activation loop and induces conformational changes associated with subsequent constitutional activation of kit in the absence of dimerization of the receptor [65]. *KIT* mutations at other codons—e.g., *KIT* mutations at the juxtamembrane domain—although frequently associated also with constitutional activation of *KIT*, are more frequently found in children than adults. Despite this variable genetic background, the clinical heterogeneity of mastocytosis presenting in some cases with anaphylaxis or variable MC mediator-related symptoms of different clinical severity could not be directly related to the *KIT* mutational profile or to the overall MC burden [66]. This notion is supported by the observation of frequent mutations in all domains of *KIT* (as assessed by mRNA sequencing) in most patients with c-MCD cases, some of them bearing multiple *KIT* mutations [67] as well as mutations in other regulatory genes relevant in MC [68, 69], similar to chronic myeloproliferative neoplasm patients that show multiple mutations in key regulatory genes in neoplastic stem cells [68, 70, 71]. Furthermore, it was recently reported that different BM MC from diagnostic and prognostic categories of SM exhibit distinct gene expression profiles, characterized by upregulation of transcription of genes involved in the innate and inflammatory immune response including adhesion molecules in indolent SM (ISM) as well as deregulation of genes associated with apoptosis and cell proliferation in patients with aggressive SM (ASM) [48]; however, anaphylaxis can present across all subtypes of SM.

Mastocytosis and Other Clonal Mast Cell Disorders

Mastocytosis is a heterogeneous group of disorders characterized by an abnormal expansion and accumulation of MC in one or multiple organs, more frequently involving the skin, bone marrow (BM), and gastrointestinal tract, among other tissues. Patients with mastocytosis have symptoms due to the release of MC mediators, the infiltration of tissues by MC, or both. The World Health Organization (WHO) defines seven categories of mastocytosis: (1) cutaneous mastocytosis (CM, when limited to the skin), (2) extracutaneous mastocytoma, (3) ISM, (4) ASM, (5) SM associated with other clonal hematological non-MC lineage diseases (SM-AHNMD), (6) MC leukemia (MCL), and (7) MC sarcoma [72, 73]. In addition, two other subvariants of indolent forms of the disease have been recognized: well-differentiated SM (WDSM) [63, 74–76] and ISMs^{-} [19, 77, 78]. According to the WHO criteria [72, 73], the diagnosis of SM is based on the coexistence of one major criterion (presence of multifocal dense aggregates of ≥15 MC in BM and/or other extracutaneous

tissues) plus one minor criterion or simultaneous detection of ≥3 of the following minor diagnostic criteria: (1) identification of morphologically atypical MC in smears or biopsy sections of BM or other extracutaneous organs, (2) aberrant expression of CD25 and/or CD2 by BM MC, (3) detection of the D816V *KIT* mutation in BM, blood, or other extracutaneous organs, and (4) sBT 20≥μg/L in the absence of other disorders associated with increased serum tryptase [79–81].

Despite the great relevance and efficiency of the WHO criteria in the diagnosis of SM, in clinical practice, the diagnosis of SM is suspected in patients with skin lesions and in patients without skin lesions with systemic symptoms of MC mediator release including anaphylaxis [72, 82]. In non-aggressive categories of SM, such as in ISMs$^-$, MC only represent a very small proportion of all nucleated BM cells (<10^{-3} BM MC, as assessed by flow cytometry) [83]. Due to the relatively low MC burden, BM MC aggregates are not found (30 % of cases) [83] in the absence of significantly increased sBT levels (<20 μg/L in 37 % of cases) [83]; so, it is mandatory to apply highly sensitive and specific methodological approaches to the study of BM MC including detailed cytological analysis of BM smears, flow cytometry immunophenotyping using specific gating strategies for detecting MC present at low frequencies in ≥10^6 cells in a sample [76, 84–86], and detection of *KIT* mutations in highly purified BM MC [19, 63].

The specific percentage of cases presenting with anaphylaxis or MC mediator-related symptoms in the absence of skin lesions of mastocytosis who are shown to have ISMs$^-$ directly depends on the sensitivity and specificity of the diagnostic methods employed, which contributes to explain the differences in the frequency of SM among adults presenting with systemic MC mediator-related symptoms in the absence of skin lesions reported in the literature [13, 19, 87, 88]. Different terms have been used to describe cases who do not strictly meet the WHO criteria for SM, despite having *KIT*-mutated clonal MC and usually expressing CD25, including (mono) clonal MC activation syndrome (MMAS) [13, 82, 87], primary MC activation syndrome (MCAS) [89], and clonal MC activation disorders (c-MCAD) [19, 90].

The clonal nature of MC in mastocytosis and other c-MCD cases can be established through demonstration of *KIT* mutations in lesional skin and/or BM cells [63, 91–94]. The *KIT* D816V mutation is the most frequent mutation found in SM, but other mutations involving exon 17 have been described such as the D816F, E839K [93], R815K [95], I817V [63], or N819Y mutations [96]; furthermore, the exon 17 D816Y [63, 93], D816H [97], insV815_I816 [63], and D820G mutations [98] have been reported in 6 % of ISMs$^-$ patients further emphasizing the need to apply highly sensitive and specific methodological approaches which are able to detect *KIT* mutations different from the typical D816V mutation MC from samples showing very low MC numbers and MC burden.

Anaphylaxis in Clonal Mast Cell Disorders

Anaphylaxis is one of the presenting symptoms in adults with ISMs$^-$, MMAS/primary MCAS/c-MCAD. The frequency of anaphylaxis is much lower in patients with ISM who have skin lesions (ISMs$^+$) (25 %), while a significant percentage of these ISMs$^+$ patients display chronic MC mediator-related symptoms without fulfilling the criteria for anaphylaxis [19].

The first case of fatal anaphylaxis in a SM patient who suffered from ASM was described in 1979 [99]. The frequency of anaphylaxis reported in adult mastocytosis (both with or without skin lesion) is much higher than that reported for the general population, ranging from 8/40 (20 %) [78] and 36/163 (22 %) [15] to 36/74 (49 %) [16] cases vs. 0.05–2 % [5–9], although there are no epidemiological studies.

The two largest series of mastocytosis patients reported so far support the notion that the prevalence of IgE-mediated allergy among patients with mastocytosis is similar to that observed for the general population [15, 16]. In both series, the majority of the anaphylactic episodes in mastocytosis were classified as idiopathic, non-IgE mediated, and/or triggered by hymenoptera sting, as also described by others [13, 19, 87, 88, 90]. Around 25 % of IgE-mediated anaphylaxis was also described, the majority of these cases (67 %) involving hymenoptera venom as a trigger [15]. The most typical triggers able to elicit MC mediator-related symptoms and anaphylaxis in c-MCD are listed in Table 1. The mean frequency of MC mediator-related symptoms reported in mastocytosis in association with nonsteroidal antiinflamatory drugs (NSAIDs) is of around 14 %[100], ranging from 8 % [16] to 11 % [15] if restricted to the frequency of anaphylaxis. Furthermore, several case reports have described anesthetic drugs as elicitors for MC mediator-related symptoms and anaphylaxis in mastocytosis, the only series reported in adult patients with mastocytosis describing a frequency of perianesthetic MC mediator-related symptoms and anaphylaxis of 10 and 0.6 %, respectively [101]. For comparison purposes, Table 2 shows the frequency of the most relevant triggers for anaphylaxis in the general population, ISMs$^-$, and c-MCAD; both drugs and foods are the most frequent triggers in the general population, whereas hymenoptera sting is the most recurrent trigger among c-MCD who present without skin lesions typical of mastocytosis.

The specific features of anaphylaxis in mastocytosis were very similar in the two largest series reported so far [15, 16]. In both series, anaphylaxis was more frequent among SM vs. CM. When ISM patients presenting with anaphylaxis evoked by hymenoptera sting or other triggers associated or not to mastocytosis skin lesions are specifically considered, no direct relationship was observed between BM MC burden as assessed by flow cytometry and the presence of BM aggregates by histopathology [90]. The most frequently observed anaphylactic symptoms involved the cardiovascular system, e.g., presyncope, tachycardia, hypotension, shock, cardiac

Table 1 Triggers of MC mediator release and MC mediator-related symptoms in c-MCD [128•]

Physical agents
Heat, changes in temperature
Friction on mastocytomas
Endoscopy
Manipulation of the GI system (e.g., during surgery)
Emotional factors
Stress, anxiety
Drugs
NSAIDs[a]
Opioids
Anesthetics[bc]
Radiological contrast media[c]
Interferon α2b
Cladribine[d]
Colloids
Insect sting and bites
Hymenoptera
Hippobosca equina, mosquito[e]

c-MCD clonal mast cell disorders, *GI* gastrointestinal, *MC* mast cells, *NSAIDs* nonsteroidal antiinflammatory drugs

[a] Frequency of MC mediator-related symptoms of 2 % in pediatric mastocytosis and 14 % in adult mastocytosis [100]

[b] Frequency of 10 % of perianesthetic MC mediator-related symptoms and 0.6 % of anaphylaxis in adult mastocytosis [101] and 0 % in children mastocytosis [129, 130]

[c] Premedication is recommended in all cases [108]

[d] Infrequent, based on one case report (J. Sheik, Beth Israel Hospital, Harvard Medical School, personal communication, September 2002)

[e] Infrequent, based on case reports [131, 132]

Table 2 Frequency of triggers of anaphylaxis in the Spanish general population vs. c-MCD patients

Trigger	General population (%) [10]	ISMs^{+a} (%)	ISMs^{-a} (%)	c-MCAD[a] (%)
Foods	34	8	6	10
Drugs	31	30	13	30
Hymenoptera	0.3	19	54	50
Anisakis	11	4	8	10
Exercise	2	0	0	0
Latex	0.6	0	0	0
Idiopathic	21	49	27	20

c-MCD clonal mast cell disorder, *c-MCAD* clonal mast cell activation disorder, *ISM*$^+$ indolent systemic mastocytosis with skin lesion, *ISMs*$^-$ indolent systemic mastocytosis without skin lesion, *MC* mast cell, *REMA* Spanish Network on Mastocytosis

[a] Data of adult population; 15, 20, and 20 % of ISMS$^+$, ISMs$^-$, and c-MCAD cases, respectively, presented anaphylaxis evoked by >1 trigger (REMA, unpublished data)

arrest; moreover, a male predominance was also found among cases with anaphylaxis and c-MCD [15, 90]. When both features are associated with anaphylaxis, they are highly suspicious for an underlying c-MCD [102]. In this regard, a scoring model has been proposed by the Spanish Network on Mastocytosis (REMA) to predict for clonal BM MC and SM in patients presenting with MC mediator-related symptoms in the absence of skin lesions due to mastocytosis [19] in which male gender and syncopal-like symptoms are included in addition to the absence of urticaria and/or angioedema during the most severe MC mediator release episode (or anaphylaxis), and sBT levels ≥25 μg/L. Such prediction model has proved to be highly efficient with a sensitivity of 92 % and specificity of 81 %, regardless of the trigger. However, it should be noted that a strong association among hypotension or syncope during anaphylaxis after hymenoptera sting and an underlying c-MCD was also described (≥90 % of cases) [90]. Overall, the REMA scoring model proved to be a significantly better predictor for the presence of clonal MC than isolated determinations of sBT levels, even when compared to the most informative sBT level cut-off (23.1 μg/L) [103••]. c-MCD can be also an underlying condition in the Kounis syndrome (50 % of cases in the largest series reported so far) [104], as defined by the association between histamine and other MC mediators released during allergic processes and the induction of coronary arterial spasm, manifested as angina [105].

In pediatric mastocytosis, a lower prevalence of anaphylaxis has been reported than in the adult population with mastocytosis ranging from 6 % [15] to 9 % [16]. Among these children, the majority of cases had idiopathic anaphylaxis (67 and 60 %, respectively), followed by anaphylaxis evoked after food intake (33 and 20 %, respectively) [15, 16], foods representing the most relevant trigger for anaphylaxis, as similarly described for the general pediatric population [4••, 10]. In contrast to adult patients, hymenoptera stings are not a frequent trigger of anaphylaxis in children with mastocytosis, where the overall frequency of IgE-mediated anaphylaxis has been reported to be of 33 % (triggered by food ingestion) [15].

Extensive cutaneous involvement was reported as a risk factor for anaphylaxis in children [16]. Severe MC mediator-related symptoms, including life-threatening symptoms requiring hospitalization or admission to a critical care unit, can be observed in pediatric mastocytosis patients with extensive skin involvement (>90 % of the body surface area) and/or elevated sBT levels (median 45.5, range 24–213 μg/L) [106]. The most frequent triggers include skin friction, heat, stress, vaccines, and fever [106, 107].

Treatment of Anaphylaxis in Clonal Mast Cell Disorders

Adequate information and training should be given to the patients, their relatives, and care providers, and an action plan

for the treatment of acute episodes following the WAO recommendations should be implemented [4••]: (1) remove the trigger if possible; (2) assess the patient's circulation, airway, breathing, mental status, and skin; (3) simultaneously, call for help and (self)inject epinephrine intramuscularly in the mid-anterolateral thigh; and (4) place the patient on the back (or in a position of comfort if there is respiratory distress and/or vomiting), with the lower extremities elevated. Supplemental oxygen should be administered, an intravenous catheter should be inserted and intravenous fluid resuscitation given, cardiopulmonary resuscitation initiated, and the patient's blood pressure, cardiac rate and function, respiratory status, and oxygenation monitored; an electrocardiogram should be performed and continuous noninvasive monitoring. Second-line medications such as H1 and H2 antihistamines, as well as corticosteroids, are also recommended in c-MCD [108•].

The aim of preventive therapy is to decrease the frequency and intensity of the episodes; the strict avoidance of triggers and antimediator therapy are strongly recommended. For each patient, the type of antimediator therapy should be carefully selected on the basis of the intensity and/or severity of the signs and symptoms observed during anaphylaxis, as well as the MC mediator-related symptoms recorded between anaphylactic episodes. Following previous recommendations, different drugs (alone or in distinct combinations) are indicated [108•, 109, 110]: (1) oral disodium cromolyn MC-stabilizer; (2) scheduled or at demand sedating H1 antihistamines (dexchlorpheniramine); (3) scheduled or at demand nonsedating H1 antihistamines, combined with a sedating antihistamine in highly symptomatic cases; (4) scheduled H2 antihistamines; (5) scheduled leukotriene antagonists; and (6) corticosteroids for uncontrolled MC mediator-related symptoms. In stress-induced anaphylaxis, a psychiatric workup followed by an adequate anxiolytic and/or antidepression therapy is recommended. Specific venom immunotherapy (VIT) is recommended in IgE-mediated anaphylaxis to hymenoptera venom; although VIT should be managed as a high-risk procedure in patients with c-MCD including mastocytosis and anti-IgE may be required in the escalating phase [111], VIT has proven effective and safe in these patients [34, 112–115], either using conventional, cluster, or rush inductions. Lifelong maintenance administration is proposed [116, 117] since cases of fatal reactions after VIT have been described after its discontinuation [118, 119]. This is supported by the practice parameters provided by the American Academy of Asthma Allergy and Immunology (AAAAI) and American College of Asthma Allergy and Immunology (ACAAI) which report patients who had previously presented severe anaphylaxis with loss of consciousness, with negative in vitro test or skin test responses after several years of VIT, but who after stopping VIT have later experienced systemic reactions (some of them fatal) to subsequent stings [120] and may likely have had underlying c-MCD. The specific frequency of systemic reactions to VIT reported in the literature are of 12 % [117] and 19 %[121] to 29 % [115]. After MC-mediators release reactions during VIT, slowing of the dose escalation together with premedication given before VIT or changes in the extract should be considered. Most importantly, between 75 and 86 % [115, 117, 121] of patients on VIT who were restung had protection from anaphylaxis. In refractory cases, with continuous and life-threatening MC mediator-related symptoms unresponsive to the antimediator therapy, treatment with anti-IgE omalizumab [122–124], hydroxiurea [125], interferon alpha 2b [126], and cladribine (2-CDA\) [127] can be effective in controlling the symptoms.

Conclusions

Mast cells from c-MCD patients usually present a constitutively altered activation-associated immunophenotype, which is also clinically reflected by symptoms related to the effect of the mediators released in tissues. *KIT* mutations in exon 17 are usually present in c-MCD, including the D816V *KIT* mutation in more than 90 % of SM patients. However, this and other less frequent *KIT* mutations do not explain the clinical heterogeneity of c-MCD. Anaphylaxis is observed in a significant proportion of all SM patients, being the presenting symptom of ISMs$^-$ and MMAS/c-MCAD/primary MCAS patients who are typically characterized by a low MC burden and absence of skin lesions of mastocytosis. The use of highly sensitive and specific methodological approaches is essential to the study of BM MC in routine laboratory diagnosis to detect the clonal *KIT* mutated, morphologically atypical, and phenotypically aberrant MC. Predominance of males and hymenoptera sting as trigger is found among adult patients with c-MCD. These patients typically present anaphylactic symptoms primarily involving the cardiovascular system in the absence of urticaria and/or angioedema, which makes such clinical presentation highly suspicious of an underlying c-MCD, particularly when occurring after a hymenoptera sting. The treatment of anaphylaxis includes adequate information and training of patients, their relatives, and care providers, the availability of individual emergency kits, the avoidance of triggers, and careful management of risk procedures able to elicit MC-mediator release. Specific antimediator therapy should be carefully evaluated in each individual patient to prevent acute episodes and to decrease the frequency and intensity of chronic symptoms.

Compliance with Ethics Guidelines

Conflict of Interest Drs. Matito, Alvarez-Twose, Morgado, Sánchez-Muñoz, Orfao, and Escribano L all declare that they have 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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- • Of importance
- •• Of major importance

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