Clinical Approach to Mast Cell Activation Syndromes: A Practical Overview

Short title: Review of mast cell activation syndromes

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Abstract

The diagnosis of mast cell activation syndromes (MCAS) is defined by 3 criteria: 1) typical clinical signs and symptoms of acute, recurrent (episodic) and systemic mast cell activation (MCA), 2) increase in tryptase level to plus 20 % + 2 ng/ml within a 1–4 hours after onset of the acute crisis, 3) response of MCA symptoms to antimediator therapy. Classification of MCAS requires applying highly sensitive and specific methodological approaches for assessing clonal bone marrow mast cells (BM MCs) at low frequencies. The Spanish Network on Mastocytosis (REMA) score is successfully used as predictive model for selecting MCAS candidates for BM studies based on a high probability of having an underlying clonal mast cell disorder (c-MCD). In this article, we propose a diagnostic algorithm and focus in the practical evaluation and management of patients with suspected MCAS.

Key words: Anaphylaxis. Antimediator therapy. Mast cell activation syndrome. Mast cell mediators release related symptoms. Tryptase.

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Resumen

El diagnóstico de síndrome de activación mastocitaria (SAM) se basa en 3 criterios: 1) signos y síntomas específicos de activación mastocitaria aguda, recurrente y sistémica, 2) aumento de los valores de triptasa en un 20 % + 2 ng/ml sobre el valor basal de cada individuo en el periodo comprendido entre 1-4 horas desde el inicio del cuadro agudo, 3) resolución de los síntomas con tratamiento antimediador. Para realizar el diagnóstico de SAM es preciso emplear métodos diagnósticos altamente sensibles y específicos capaces de detectar bajas cantidades de mastocitos en la médula ósea. El modelo predictivo de la Red Española de Mastocitosis (REMA score) resulta útil para identificar a los pacientes con mayor probabilidad de padecer una patología mastocitaria clonal y que por tanto requieren que se realice un estudio de médula ósea en el proceso diagnóstico. En este artículo, proponemos un algoritmo diagnóstico para SAM y abordamos el manejo de estos pacientes desde un punto de vista práctico en la consulta alergológica.

Palabras clave: Anafilaxia. Síndrome de activación mastocitaria. Síntomas secundarios a la liberación de mediadores mastocitarios. Tratamiento antimediador. Triptasa.

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Introduction

Mast cells (MCs) are myeloid lineage derived cells. They are present in connective tissues and play an important role as immunomodulatory and effector cells by releasing several mediators that provoke clinically relevant reactions[1-3]. The correct diagnosis of mast cell activation syndrome (MCAS) is usually a challenge for the clinicians, since other conditions that mimic MCAS should be ruled out (i.e. cardiovascular, endocrinologic, gastrointestinal, rheumatologic and immunologic disorders, among others)[4]. Frequently, symptoms of mast cell activation (MCA) are nonspecific and can present in diverse physiologic and pathologic conditions. Thus, MCAS must be considered as an unusual entity and may be diagnosed according to the following criteria [2,5,6]: 1) acute, recurrent (episodic) and systemic (involving at least 2 organ systems) signs and symptoms of MCA consistent with the diagnosis of anaphylaxis; 2) an increase in tryptase level from the individual's baseline to plus 20 % + 2 ng/ml within a 1–4 hours after onset of the reaction; and 3) clinical response to therapy with MC-stabilizing agents that target MC mediator production, secretion or receptor binding. All three criteria must be fulfilled to establish the diagnosis of MCAS. Despite their great utility, they also present some limitations. Furthermore, MCAS and its diagnostic criteria are primarily reported in the adult population, so further studies are required for the evaluation of this entity in pediatric population[7].

Clinical signs and symptoms of MCAS[2,3,8]

MCA symptoms are secondary to the release of several different vasoactive and pro-inflammatory MCs mediators such as histamine, prostaglandins (PGs), leukotrienes (LTs), proteases, platelet-activating factor (PAF), growth factors, and cytokines, among others. Different combinations of these mediators may be involved in MCA-related

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symptomatology that can present as acute episodes and/or chronic evolution. The severity of MCA symptoms may range from mild to severe, and even life-threatening in some cases. Moreover, the symptoms may be elicited either by identified triggers (IgE or non-IgE mediated) or may be unknown. Thus, the clinical presentation of MCAS is very heterogeneous[9].

The clinical symptoms of diagnostic value in MCAS are grouped in the following organ systems[3,8]:

1) Cardiovascular: hypotension, tachycardia, dizziness or syncope.

2) Gastrointestinal: crampy abdominal pain, diarrhea, nausea, and vomiting.

3) Dermatologic: urticaria, angioedema, pruritus, and flushing.

4) Respiratory: wheezing, shortness of breath, and inspiratory stridor.

It should be emphasized that none of the above mentioned symptoms are completely specific for MCAS. In fact, at least 2 organ systems need to be concurrently involved in acute recurrent symptomatic crisis to fulfill the clinical criteria of MCAS (consistent with the working diagnosis of anaphylaxis). However, the clinical presentation of dizziness or syncope in a male triggered by hymenoptera sting is highly suspicious to be related to a clonal mast cell disorder (c-MCD)[8,10]. On the other hand, recent reports by specialized working groups on the topic[2,3] recommend not to consider for diagnosis purposes some of the non-specific symptoms previously included (i.e. nasal congestion, headache, neurologic symptoms, and fatigue)[2,11,12] nor other manifestations and conditions that lack precision for the diagnosis of MCAS or are not clearly related to MCA (i.e. fibromyalgia-like pain, dermographism, tired appearance, chronically ill appearance, rashes of many sorts, prostatitis, different psychiatric and neurologic disorders, Ehlers-Danlos syndrome, and postural orthostatic tachycardia syndrome -POTS-, among others[3].

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Independently of the clinical picture, an appropriate evaluation of the symptoms or condition in each patient is mandatory. This should be done according to evidence-based medical standards and performing a complete differential diagnosis[4]. Therefore misdiagnosis of MCAS or other concomitant pathologies even when the diagnosis of MCAS is well established, would be avoided.

MC mediators monitoring in the diagnosis of MCAS on clinical basis

The MC mediators used as biomarkers of MCA in different disorders (i.e. including allergen-triggered systemic anaphylaxis, systemic anaphylaxis associated to systemic mastocytosis –SM-, aspirin-exacerbated respiratory disease, among others) include tryptase (either on serum or plasma), urine histamine metabolites (N-methylhistamine -N-MH- and N-methylimidazole acetic acid -MIAA-); and, the urine metabolites of prostaglandin D2 (PGD2) and leukotriene C4 (LTC4): 11β-PGF2α and LTD4/LTE4, respectively[3,6,13].

Histamine and tryptase are both produced and stored in tissue MCs and blood basophils. However MCs contain more than 100-fold higher levels of tryptase than basophils[14]; and inmature (leukemic) basophils express relatively low amounts of tryptase[15]. Indeed, other cells can release histamine (i.e. neutrophils, platelets, histamine-secreting carcinoid tumors) that is metabolized rapidly (half-life 1-2 minutes) reducing the utility of this mediator as a clinically useful biomarker[13]. Despite this fact, some authors consider histamine-specific metabolites (N-MH, and MIAA) as appropriate biomarkers of systemic histamine release from MCs or basophils[13,16], although in one study [17] the measurement of 24-hour urine N-MH was elevated only in 2/25 MCAS patients, and showed little clinical utility for diagnosing MCAS.

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Although MCs are the major source[13] of the previously mentioned mediators, there are other cell types releasing such substances. PGD2 can be mainly produced by Th2 lymphocytes, dendritic cells, megakaryocytes and eosinophils; prostaglandin F2 (PGF2) is also synthesized by the luteal endometrium, gestational tissues, human and primate granulosa cells, and hepatocytes; and LTC4 can be generated by basophils, eosinophils, monocytes, macrophages and platelets[3,13]. Thus, among all these mediators, serum tryptase is considered the most precise parameter for the evaluation of MCA[2], being the biomarker employed as a MCAS criterion.

The commercially available assay (ImmunoCAP Tryptase, Thermo Fisher Scientific) detects total tryptase. Of note, α-protryptase is released constitutively from MCs into the plasma[18], while a specific release of β-tryptase during anaphylaxis has been reported[19]. Increased tryptase levels in anaphylaxis evoked by insect stings frequently correlate with the magnitude of hypotension during the episode. Furthermore, hypotension in anaphylaxis elicited by hymenoptera sting is highly suspicious for an underlying c-MCD[3,9,20-24].

A relationship between increased serum tryptase levels, either acute tryptase or acute/basal ratio (preferable), detected during perioperative anaphylaxis and an underlying IgE-mediated anaphylaxis is also described[25-27]. On the other hand, when anaphylaxis is triggered by foods the ratio acute/basal is more informative than peak tryptase determinations (usually in the normal range)[3,28-30].

Regarding postmortem serum tryptase, levels can be elevated in non-anaphylactic causes of death (i.e. myocardial infarction, asphyxia, or trauma) [31,32].. A recent study established the postmortem tryptase reference range in non-anaphylactic death as < 23 μg/l [31]. In addition, tryptase levels can vary depending on several perimortem as

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postmortem factors including the sampling technique: it is recommended to take blood samples from a clamped femoral/external iliac vein[31].

After a suspicious MCA episode is recommended to analyse serum tryptase levels in the following 1-4 hours, and this result must be compared to the previous individual´s serum baseline tryptase and/or determine the baseline levels at least 24-48 hours after the resolution of the clinical event (following the 20 %+2 formula)[6,33,34]. Noteworthy, the sensitivity of this tryptase algorithm decreases with decreasing clinical severity and with delayed blood extractions after the resolution of clinical symptoms[2]. Tryptase can be captured and analyzed in a blood sample. However, other mediators measurements require a period of 24 hours (i.e. urine samples) following specific guidelines including dietary restrictions (i.e. histamine metabolites)[16,17]. On the other hand, a serum tryptase analysis immediately after a MCs crisis may be difficult to obtain due to logistic concerns (i.e. frequently it is not routinely performed in the emergency room set); so, in the author's opinion it is advisable to provide specific written instructions for the determination of serum tryptase to patients at risk to present acute MCA crisis who require attention at the emergency room.

Although, it is reported that metabolites of PGD2 and cys-LTs (LTC4, LTD4 and LTE4) can be measured on random urine specimens[13] and serum samples[35], the commercial assays to perform these analysis may not be available in some clinical settings. In addition, they can be elevated in different reactive conditions (cell source might be ambiguous) and in mild mediator-related symptoms[2,3,6]. Thus, their contribution in the diagnosis of MCAS is not well defined; although some authors report their usefulness in guiding treatment that blocks the production of MC mediators [13].

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Other parameters such as diamino-oxidase (DAO) and heparin are not recommended as biomarkers of MCAS at this moment[3,6].

The hereditary α-tryptasemia (HαT) is an autosomal dominant disorder characterized by increased copy numbers of the *TPSAB1* gene encoding α-tryptase reported in 4-8% of the general population[36-39]. A gene-dose effect between the number of α-tryptase genes (assessed in buccal swab[3], peripheral blood or bone marrow –BM-[36]) and basal serum tryptase levels and severity of clinical symptoms, respectively, is reported[37,39]. HαT can occur in apparently healthy individuals with (slightly) elevated basal serum tryptase, but also associated with symptoms suggestive of autonomic dysfunction, flushing, pruritus, gastroesophageal reflux, joint hypermobility, arthralgia, irritable bowel syndrome, retained primary dentition, and immediate hypersensitivity reactions, among others. Interestingly, HαT has also been described in clonal MC disorders (c-MCD)[39] and mastocytosis patients, more frequently among cases with hymenoptera venom hypersensitivity reactions and severe cardiovascular mediator-related symptoms/anaphylaxis; so,HαT has been proposed as an emerging biomarker in mastocytosis for determining the individual patient´s risk of developing severe anaphylaxis[36]. Nevertheless, further studies are required to establish the role of HαT in MCAS.

Therapeutic options for MCA symptoms

Anti-mediator therapy aims at inhibiting production, interfering with release, blocking the specific receptors, or antagonizing the effects of MCs mediators; and it is used both to treat and to prevent acute and chronic MCs mediator release-associated symptoms[40].

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Due to the great heterogeneity of the clinical picture of MCAS (intensity, severity, identified trigger, unprovoked, etc.) the treatment of patients with MCAS is individualized using a combination of different drugs, doses and administration schedules (on demand or continuous administration) in order to control the symptoms and the underlying pathology.

On demand schedule is used to control acute MCA episodes and in the most severe cases correspond to acute treatment of systemic anaphylaxis[29]. It consists on: 1) remove the trigger when possible; 2) assess the patient's circulation, airway, breathing, mental status, and skin; 3) place the patient in supine position (or in a position of comfort if there is respiratory distress and/or vomiting), with the lower extremities elevated; 4) call for help and (self) inject epinephrine intramuscularly in the mid-anterolateral thigh. Consider, if necessary, supplemental oxygen, intravenous fluids, cardiopulmonary resuscitation, and continuous non-invasive monitoring. In addition, intramuscular epinephrine is also indicated in laryngeal angioedema, and in severe bronchospasm (also treated with inhaled rapidly acting β2 agonist)[3].

Second line medications, such as H1 and H2 antihistamines, as well as corticosteroids, are also recommended in the treatment of anaphylaxis or acute MCA episodes[8,40]. Patients at risk for such events, as well as their relatives and care providers, should carry an epinephrine injector and be trained in the treatment of acute episodes.

As regards the prevention of presentation of MCA related symptoms is important to avoid or manage adequately the general and specific triggers in each case that may elicit MC mediators release (e.g. hymenoptera venoms, non-steroidal anti-inflammatory drugs –NSAIDs-, opioids, anesthetic procedures, iodinated contrast media, etc.)[3,40,41].

Furthermore, continuous antimediator therapy should be selected according to intensity and/or severity of the MCA signs and symptoms observed in each patient. Evaluating

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the possible MC mediator-related symptoms recorded between acute systemic MCA (anaphylactic) episodes, will also be relevant.

Following previous recommendations, based on mastocytosis experts´ practice[3,8,9,42-44], different drugs (alone or in distinct combinations) are indicated: 1) oral sodium cromolyn MC-stabilizer; 2) scheduled or at demand non-sedating H1 antihistamines (preferable), combined with a sedating antihistamine at night or on demand in selected highly symptomatic cases[44,45]; 3) scheduled H2 antihistamines; 4) scheduled leukotriene antagonists; and 5) corticosteroids for uncontrolled MC mediator-related symptoms. Table 1 shows a stepwise antimediator therapy approach to control MC-mediators related symptoms.

Despite there is little high-quality evidence based on well-designed, double-blind, and placebo-controlled randomized trials (DBPCRT) to support recommendations regarding choice of H1-antihistamine or dosing[46], some interesting data regarding this topic have been reported. Desloratadine and ketotifen have MC stabilizing properties[47,48]. Loratadine in addition to its antimediator activity, inhibits *in vitro* spontaneous growth of neoplastic MC[49]. Platelet-activating factor (PAF) is a lipid-derived mediator involved in episodic hypotension and flushing in mastocytosis[50]; rupatadine exert an antagonistic effect against PAF receptor[51] and improves quality of life and MC-related symptoms (i.e. itch, wheal, flare, flushing, tachycardia) in mastocytosis patients based on DBPCRT[50]. Furthermore, rupatadine and levocetirizine (in less extent) inhibit *in vitro* induced platelet-activating factor (PAF) degranulation in MC[52].

H2 antihistamines are specifically used for treating gastric hypersecretion and peptic ulcer-related symptoms in patients with mastocytosis, and they can also enhance the H1 antihistamines effect and be useful in patients with abdominal pain, diarrhea, and recurrent, severe MC mediator release episodes[45,53-56].

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The precise mechanism of action of sodium cromolyn, a MC stabilizer, remains unclear. However, it inhibits MC activation and MC release of mediators *in vitro* and *in vivo*, the GTP-g-S-induced exocytosis of MCs and modulates sensory nerve function[57,58]. Moreover, despite its limited systemic absorption[59] oral sodium cromolyn is effective to control gastrointestinal symptoms (based on double-blind, placebo-controlled trials) such as abdominal pain, vomiting or diarrhea. In addition to other clinical manifestations related with the release of MC mediators, including pruritus and flushing, among others[54,60-64]. The Spanish Network on Mastocytosis (REMA), based on its experience, recommends the use of oral disodium cromolyn as treatment for chronic/recurrent MCA symptoms such as flushing, abdominal cramping, diarrhoea, and unprovoked anaphylaxis[8,44,53]. Standard doses of oral disodium cromolyn for adult population are 600-800 mg/day, although they could be up to 1600 mg/day if necessary[44].

Acetylsalicylic acid (ASA) might control flushing and hypotension in selected cases with known tolerance to the drug and elevated urinary 11β-$PGF_{2\alpha}$[3]. Celecoxib could be considered as an option to treat intractable diarrhea in mastocytosis patients[65]. Montelukast showed usefulness to improve respiratory, cutaneous and gastrointestinal symptoms in mastocytosis patients[66-68].

Systemic corticosteroids administration must be limited due to side effects for long-term use. They are recommended for refractory, acute and/or severe MC mediator release related symptoms. Corticosteroids can improve abdominal pain uncontrolled with other therapies; short cycles of either low doses of prednisone (0.3 mg/Kg/day) or oral budesonide (0.1 mg/Kg/day) may be prescribed[8,44,54,69].

Indeed, anti-IgE therapy with omalizumab has been useful in cases with anaphylaxis unresponsive to conventional antimediator therapy[3,8,9,40], as well as for reaching

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maintenance doses of venom immunotherapy (VIT)[70]. VIT is recommended in IgE mediated hymenoptera anaphylaxis with an extended maintenance administration (lifelong)[71,72].

Currently, there is no consensus regarding recommendations about the antimediator therapy stepwise, nor the number of therapies or specific combinations to establish lack of response. The REMA defines the lack of response to antimediator therapy after failure to, at least, a combination of oral cromolyn, H1 and H2 antihistamines, antileukotrienes, and ASA (or other cyclooxygenase inhibitors)[8].

A provisional diagnosis of "possibly MCAS" may be established in patients who present with acute, systemic and recurrent MCA symptoms and a diagnostic increase in serum tryptase levels, in the absence of improvement with conventional antimediator therapy that should be increased[2].

Bone mass loss, specifically osteoporosis, constitutes an important public and treatable health problem that should be evaluated in clonal MCs pathology. It is a frequent finding in systemic mastocytosis (moreover among patients without cutaneous involvement)[10,73], secondary to local MCs infiltration and disturbances in bone remodeling, due to MCs mediators such as IL-6, histamine and heparin[74,75]. Calcium, vitamin D supplements and biphosphonates are therapies usually prescribed[76]. On the other hand, denosumab[77] or interferon alpha-2b[78,79] might be also considered in patients with severe osteoporosis at risk of pathologic bone fractures unresponsive to conventional treatments.

Classification of MCAS

The current classification of MCAS establish the following categories: 1) primary MCAS where *KIT*-mutated, clonal (CD25+) MCs are detected (with or without an

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underlying diagnosis of mastocytosis); 2) secondary MCAS in which usually an IgE-dependent allergy, another hypersensitivity reaction or another immunologic disease that can evoke MCA is detected; and 3) idiopathic MCAS, when neither *KIT*-mutated MCs, nor other inflammatory disorders that may explain MCA, nor a trigger for a hypersensitivity reaction is found[2].

According to the REMA experience, around 5% of patients presenting with anaphylaxis in the absence of the typical skin lesions for mastocytosis may have an underlying clonal MCAS (c-MCAS)[80]. When MCAS diagnostic criteria are fulfilled, the evaluation of the typically D816V *KIT* mutation (or other gain-of-function *KIT* mutations)[81] should be considered. Usually, a bone marrow (BM) MCs immunophenotyping is necessary to confirm or rule out a primary (clonal) MCAS. Some REMA data suggest a higher utility in the detection of the D816V *KIT* mutation as assessed by allele-specific oligonucleotide quantitative polymerase chain reaction (ASO-qPCR) in fluorescence-activated cell sorting (FACS)-purified BM MCs rather than in peripheral blood or unfractionated BM samples[8]. If there is no evidence of clonality (CD25- BM MCs and no *KIT* mutations), a non-clonal MCAS (nc-MCAS) should be considered, although the term non-clonal is based on the absence of clonality currently detectable[40].

Furthermore, clonal or not, according to the clinical features, the identification of co-existence of allergy or other underlying conditions should be evaluated (Table 2)[8,9,40]. Thus, cases who present as IgE-mediated anaphylaxis after hymenoptera sting and associate an underlying c-MCD could be more specifically categorized[8,10,40,82].

It is noteworthy that MCAS patients with associated skin lesions usually correspond to a c-MCD, either cutaneous mastocytosis or SM[8]. In this line, it has been recommended

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to use the diagnostic label 'SY' –symptoms- (i.e. indolent SM -ISM_{SY}-) in mastocytosis cases, with any form of MCA requiring continuous antimediator therapy, even if the criteria of MCAS are not met[2,33].

Bone marrow aspirate and biopsy: how and when?

The BM study does not quantify the MCs activation and it is not necessary to be performed before starting antimediator therapy. It is well known that mastocytosis (or c-MCD) patients present a remarkable clinical heterogeneity in the severity of MCs mediator-related symptoms[9]. On the other hand, cytorreductive and/or targeted therapies should not be started in the absence of a complete BM study including the mutated *KIT* status[3,9,40].

The evaluation of patients with suspected or confirmed MCAS diagnosis should include a clinical, physical and allergological work-up together with a routine peripheral blood (PB) count and differential, routine biochemistry and serum baseline tryptase (sBT). In addition, the BM study is mandatory for the classification of MCAS (see Table 2), and in order to diagnose an underlying c-MCD in the absence of the typical skin lesions of mastocytosis (c-MCAS or SM) [9,40]. It is also reported a relatively low MCs burden in c-MCAS and indolent systemic mastocytosis without skin lesions of mastocytosis. (ISMs-)[9,40,73]. Usage of highly sensitive and specific methodological approaches to study BM MCs are required including detailed cytological analysis of BM smears, histology and immunochemistry, flow cytometry immunophenotyping using specific gating strategies for detecting MCs present at low frequencies. Indeed, allele-specific oligonucleotide-quantitative polymerase chain reaction (ASO-qPCR) on unfractionated BM and highly (fluorescence-activated cell sorting –FACS-) purified BM MCs techniques for detection of *KIT* mutations[81]. In case these latter failed, the mutation

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could be also explored by peptide nucleic acid (PNA)-mediated PCR clamping in FACS-purified BM MCs. Finally, another useful option is sequencing of the whole *KIT* gene[8]. Usually these complete methods are only available in reference centers that have a higher efficiency in the diagnosis of c-MCD[83].

Some predictive models such as the REMA score[73,84,85] or the National Institutes of Health clinical activity score (including allele-specific D816V *KIT* PCR on peripheral blood)[86] have shown to be useful for selecting MCAS candidates for BM studies based on a high probability of having an underlying c-MCD. The REMA score (Table 3) is based on gender, the symptoms and signs observed during the acute episodes, and sBT levels. Here we show 2 brief examples of how to use the REMA score to evaluate each systemic acute episodes in adult patients in the absence of skin lesions of mastocytosis (some cases can present different episodes with different MCA-related symptoms every time): 1) A 35-y.o. man who presented with dizziness and loss of consciousness after a wasp sting, the allergological work-up showed sensitization to *Polistes dominula* venom and a sBT of 10 ng/ml; the REMA score is 4: male (+1), no urticaria, no pruritus and no angioedema (+1), syncope (+3), and sBT < 15 ng/ml (-1). 2) A 35-y.o. man who presented with generalized urticaria, throat swelling, bronchospasm, abdominal cramping and diarrhea without any identified trigger after a thorough allergological work-up, and a sBT of 22 ng/ml; the REMA score is -1: male (+1), urticaria and angiodema (-2), and sBT not applicable.

Figure 1 depicts a proposed algorithm for the diagnosis of MCAS patients. A REMA score ≥ 2 predicts with a high sensitivity and specificity for ISMs- or c-MCAS and the BM study is indicated. On the other hand, a REMA score < 2 usually indicates non-clonal disease, in this situation, if sBT levels are < 25 - 30 ng/ml it is recommended searching for the *KIT* D816V mutation by ASOqPCR in peripheral blood (PB) and, if

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positive, then a study of the BM would be also indicated. Finally, the European Competence Network on Mastocytosis (ECNM) recommends to perform a BM study in cases with sBT ≥ 25 - 30 ng/ml; in these cases, SM as well as another bone marrow clonal diseases (i. e. myeloproliferative neoplasm, myelodysplastic syndrome or a myeloid leukaemia), renal failure, genetic syndromes (i.e. HαT) among others, should be also evaluated[85].

Conclusions

This article describes/ details the recommendations for the diagnosis and management of MCAS according to the latest studies and consensus guidelines. MCAS diagnosis is based on 2 clinical and 1 analytical (blood sample) achievable criteria in a routine basis. The subsequent classification is based on the presence of clonal or non-clonal BM MCs, frequently is only available in specialized centers. In addition, other underlying conditions (i.e. allergy) should be evaluated according to the clinical picture in each case. Patients with MCAS usually require assistance by multidisciplinary teams, due to the great heterogeneity in clinical presentation and the methodological approaches required in the management and classification of these cases. As future directions, further studies and advances are necessary to determine the frequency of MCAS in adult and pediatric population, to specify and standardize clinical recommendations about antimediator therapy stepwise. Also it is essential to address other aspects such as the definition of the criteria to characterize the lack of response to antimediator therapy, to improve the measurement and monitoring of other MCs mediators different from tryptase, to understand the relevance of increased copy numbers of *TPSAB1* gene in MCAS, to improve the efficiency in the detection of *KIT* mutation in peripheral blood, and to better characterize non-clonal MCAS.

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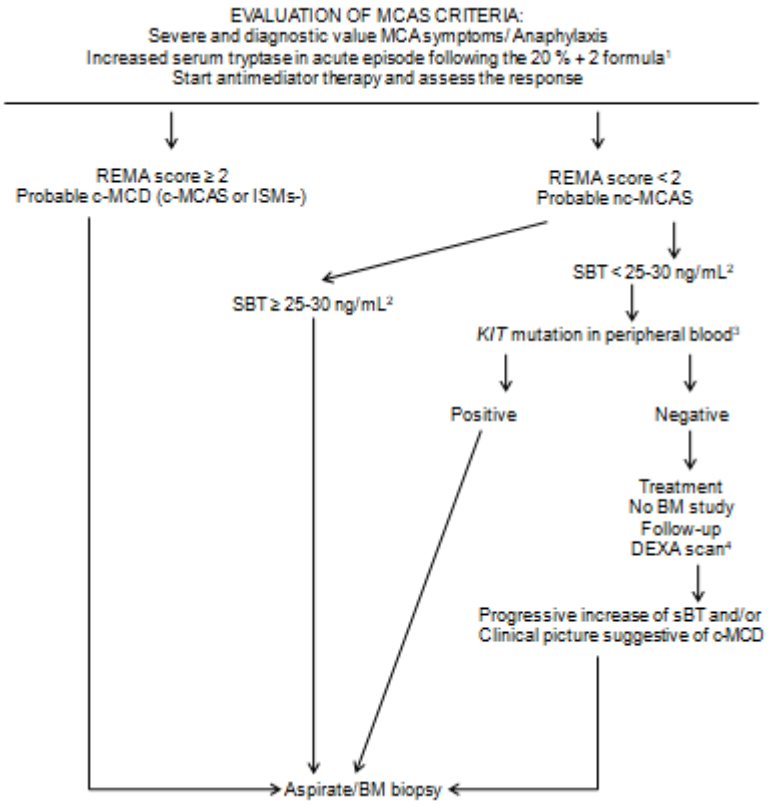
Tables and Figures

Figure 1. SEAIC proposed algorithm for the diagnosis, management and follow-up of MCAS patients, based on REMA, ECNM and AAAAI recommendations [3,40,85].



Highly sensitive diagnostic approaches are mandatory to detect a low burden of pathological (clonal) BM MCs, as could be expected in cases with a REMA score ≥ 2 and low sBT levels. 1. Elevation of other validated MCs mediators could be considered for evaluation. 2. sBT values are based on previous algorithm recommendations[85]. 3. *KIT* D816V mutation by ASOqPCR in peripheral blood; negative results related to a low allelic mutation burden should be considered [87,88]. 4. Bone mass loss is a frequent finding in SM, secondary to the release of MCs mediators[40].

Evaluation of HαT could be considered in cases with elevated sBT and/or cardiovascular/anaphylaxis MCs-mediators related symptoms.

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AAAAI, American Academy of Allergy Asthma and Immunology; ASOqPCR, allele-specific oligonucleotide-quantitative polymerase chain reaction; BM, bone marrow; c-MCAS, clonal mast cell activation syndrome; c-MCD, clonal mast cell disorder; DEXA, dual-energy x-ray absorptiometry; ECNM, European Competence Network on Mastocytosis; HαT, hereditary alpha tryptasemia; ISMs-, indolent systemic mastocytosis without skin lesion; MCA, mast cell activation; MCAS, mast cell activation syndrome; MC, mast cells; nc-MCAS, non-clonal mast cell activation syndrome; REMA, Spanish Network on Mastocytosis; sBT, serum basal tryptase; SEAIC, Sociedad Española de Alergología e Inmunología Clínica; SM, systemic mastocytosis; VIT, venom immunotherapy.

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Table 1. Antimediator therapy stepwise approach for MCs mediators related symptoms in MCAS[3,8,40,42,43]		
Symptoms	Therapy for chronic/recurrent symptoms	Therapy for acute episodes
Pruritus, urticaria and/or angioedema	Non-sedating H1, up to four-fold doses +Topical cromolyn, if skin lesions or pruritus are restricted to small areas +Oral cromolyn +Omalizumab, if uncontrolled CSU ± Sedating H1, if uncontrolled episodes ±Systemic corticosteroids*	Non-sedating H1 +Topical cromolyn, if skin lesions or pruritus are restricted to small areas ± Sedating H1 ±Systemic corticosteroids +Epinephrine, if acute laryngeal angioedema
Flushing	Oral cromolyn + Non-sedating H1 +H2 ±ASA, if previous tolerance is demonstrated ± Sedating H1 ± LT antagonists	Non-sedating H1 ± Sedating H1 ±Systemic corticosteroids
Abdominal cramping and/or diarrhoea	Oral cromolyn +Non-sedating H1 ± H2 ± Oral budesonide cycles ±LT antagonists ±COX2-I, if previous tolerance is demonstrated ±Low doses of systemic corticosteroids cycles	Non-sedating H1 ± Sedating H1 ± Oral budesonide ± Antispasmodic drugs, if acute episodes of pain ±Antidiarrheal drugs; if acute, severe and uncontrolled episodes of diarrhoea** ±Low doses of systemic corticosteroids
Peptic symptoms	Oral cromolyn + H2 +PPI	H2 +PPI
Anaphylaxis†	Oral cromolyn +VIT, if hymenoptera venom allergy§ +Non-sedating H1 + H2, if idiopathic, stress-induced or uncontrolled anaphylaxis +Anxiolytics or antidepressants, if stress-induced anaphylaxis ±Sedating H1, if stress-induced anaphylaxis +Omalizumab, if uncontrolled anaphylaxis or bad tolerance to	Epinephrine ±Non-sedating or sedating H1 ± Systemic corticosteroids ±H2 +Inhaled short β2 agonist, if bronchospasm ± Fluids ± Vasoactive drugs

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	VIT ±IFN* ±TKI*	

* In unresponsive selected cases
**Evaluate known tolerance if an opioid drug is prescribed
†Avoidance of the specific trigger in food or drug anaphylaxis
§Some cases may not require associated cromolyn treatment
ASA, acetylsalicylic acid; COX2-I, cyclooxygenase 2 inhibitor; CSU, chronic spontaneous urticaria; H1, H1 antihistamine; H2, H2 antihistamine; LT, leukotriene; MC, mast cells, MCAS, mast cell activation syndrome; PPI, proton pump inhibitor; TKI, tyrosin-kinase inhibitor; VIT, venom immunotherapy

Table 2. Classification of Mast Cell Activation Syndromes[2,8].

Molecular category	Recognized category	Diagnostic MCs features	Underlying conditions
Clonal MCs	Primary	D816V *KIT* mutation* and/or aberrant CD25+ BM MCs expression (WHO minor SM criteria)	c-MCAS (or MMAS)
		WHO criteria for SM are fulfilled	SM
		Infiltration of skin by MCs, in the absence of WHO criteria for SM**	CM
Non-clonal MCs	Secondary	No *KIT* mutations detected† CD25- BM MCs expression	IgE-mediated allergy, another hypersensitivity reaction, or another immunologic (autoimmune, inflammatory) disease that evoke MCA
	Idiopathic	No *KIT* mutations detected† CD25- BM MCs expression	Neither primary nor secondary conditions are found

BM, bone marrow; CM, cutaneous mastocytosis; c-MCAS, clonal mast cell activation syndrome; MCs mast cells; MCA, mast cell activation; MCAS, mast cell activation syndrome; MMAS, monoclonal mast cell activation syndrome; SM, systemic mastocytosis; WHO, World Health Organization.
*Other gain-of-function *KIT* mutations are described[3,81].
**Skin MC infiltrate is accepted to be a clonal MC proliferation.
†Potential existence of unknown molecular defects cannot be ruled out.
Adapted with permission from Elsevier[8].

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Table 3. REMA score		
Variable		Score
Gender	Male	+1
	Female	-1
Clinical symptoms	No urticaria, no pruritus and no angioedema	+1
	Urticaria, pruritus and/or angioedema	-2
	Presyncope or syncope	+3
sBT	< 15 ng/mL	-1
	> 25 ng/mL	+2
Score < 2: low probability of clonal MCAS Score ≥ 2: high probability of clonal MCAS Sensitivity: 0.92; Positive Predictive Value: 0.89; Specificity: 0.81; Negative Predictive Value: 0.87 MCAS, mast cell activation syndrome; REMA, Spanish Network on Mastocytosis; sBT, serum basal tryptase. Reproduced with permission from Elsevier and Karger[73,84].		