



Perspective

Mast cell activation syndromes and anaphylaxis

Multiple diseases part of the same spectrum

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Anaphylaxis represents the most severe clinical expression of mast cell (MC) activation. Recent advances in the understanding of MC physiopathology have shown that clonal MC disorders are associated with increased risk of anaphylaxis vs the general population.¹ A subgroup of patients suffer from MC-mediator release symptoms without known genetic (primary) or secondary causes of MC activation. In an attempt to unify and classify all those entities that can occur underlying anaphylaxis, the concept of MC activation syndrome (MCAS) has recently emerged.¹

The term MCAS encompasses a group of diseases defined by the following criteria¹: 1) typical, recurrent, and frequently severe clinical signs or symptoms of MC activation; 2) clinical response to MC-stabilizing or antimediator drugs; and 3) increase in the levels of MC mediators. According to current consensus recommendations, all 3 criteria must be fulfilled to establish the diagnosis of MCAS. However, each of these criteria has pitfalls that might contribute to misdiagnosis of MCAS.

Mast cell activation symptoms are produced by a wide variety of mediators released from MCs, including histamine, prostaglandins (PGs), leukotrienes (LTs), proteases, platelet-activating factor, growth factors, and cytokines, which exhibit vasoactive, smooth muscle, and mucus-stimulating properties. Thus, the clinical picture of MCAS is nonspecific and highly heterogeneous. Some authors have suggested that the diagnosis of MCAS is more likely when symptoms involve at least 2 organs among the cardiovascular, respiratory, dermatologic, and gastrointestinal systems.² However, isolated cardiovascular symptoms (ie, dizziness or loss of consciousness), presenting in an appropriate scenario

(eg, male who suffers hymenoptera sting) are closely related to clonal MCAS. By contrast, when symptoms develop in the absence of the other aforementioned proposed criteria, the clinical picture is less likely to correspond to MCAS.²

Other limitation of the proposed criteria for MCAS is that response to antimediator therapy and the number of therapies or specific combinations of MC-stabilizing or antimediator drugs required for establishing lack of response are not clearly defined. Considering the variety of clinical manifestations of MCAS, and that many of the symptoms can be caused by different mediators, lack of response to antimediator drugs should be established only after demonstration of treatment failure to, at least, a combination of oral cromolyn, H1 and H2 antihistamines, anti-leukotrienes, and aspirin (or other cyclooxygenase inhibitors). Whenever the clinical picture is highly suggestive of MC activation, we recommend using these drugs in a rational, stepwise fashion. Indeed, some patients who are refractory to conventional antimediator therapy can benefit from omalizumab. Table 1 shows an overview of the general management of patients with MCAS based on the Spanish Network on Mastocytosis (REMA) recommendations.

Regarding biochemical markers, an increase in tryptase levels greater than 20% of baseline plus 2 µg/L in a blood sample obtained within a 1- to 4-hour interval since the beginning of symptoms is the more specific approach to demonstrate MC activation.¹ By contrast, no consensus has been reached yet on the minimal increase of mediators such as histamine, PGD₂, 11β-PGF_{2α}, LTC₄, or LTE₄ needed to support MC activation.² It should be also noted that MC mediators for which no assays are currently available can be also involved in MCAS.² Moreover, a determination of tryptase during an acute episode of MC activation may be difficult to obtain because of logistic concerns.

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Table 1
Pharmacological Approaches Recommended by the REMA as Baseline Therapies for the Most Relevant Mast Cell-Mediator Release Symptoms and Their Treatment during Acute Episodes in Adult Patients with MCAS

Symptoms	Baseline therapy for patients with chronic/recurrent symptoms			Treatment of acute episodes		
	1 st line	2 nd line	3 rd line	1 st line	2 nd line	3 rd line
Skin						
Pruritus, urticaria or angioedema	Nonsedating H1	+ H2 ± Sedating H1	+ Oral DSCG ± Rupatadine ± Systemic CS ± Omalizumab ^a	Sedating H1 Topical DSCG ^b	+ H2 ± Topical CS	+ Systemic CS
Flushing	Oral DSCG + nonsedating H1	+ H2 ± Sedating H1	+ Rupatadine ± ASA ^c ± LT antagonists	Sedating H1	+ H2 ± Systemic CS	+ ASA ^c
Gastrointestinal						
Abdominal cramping	Oral DSCG	+ Nonsedating H1 ± H2	+ ASA ^c ± LT antagonists ± Low doses of oral CS	Sedating H1	+ H2 ± Oral BDS	+ Systemic CS ± NSAIDs ^c ± Opioids ^c
Diarrhea	Oral DSCG	+ Nonsedating H1 ± H2	+ LT antagonists ± NSAIDs ^c , COX2-I ± Low doses of oral CS	Sedating H1	+ H2 ± Oral BDS	+ Systemic CS
Peptic symptoms	Oral DSCG + H2	+ PPI ± H1		H2	+ PPI	
Anaphylaxis						
Idiopathic anaphylaxis	Oral DSCG + nonsedating H1 + H2	+ Sedating H1 ± Rupatadine	Omalizumab ^e IFN ^e TKI ^e	Epinephrine ^d	+ Systemic CS ± Sedating H1 ± H2	
Hymenoptera-induced anaphylaxis	Oral DSCG + VIT ^f	+ Nonsedating H1 + H2		Epinephrine ^d	+ Systemic CS ± Sedating H1 ± H2	
Stress-induced anaphylaxis	Oral DSCG + nonsedating H1 + H2 + Anxiolytics or antidepressants	+ Sedating H1 ± Rupatadine	Omalizumab ^e TKI ^e	Epinephrine ^d	+ Systemic CS ± Sedating H1 ± H2	
Food- or drug-induced anaphylaxis	No specific treatment is recommended, except avoidance of the culprit agent.			Epinephrine ^d	+ Systemic CS ± Sedating H1 ± H2	

Abbreviations: ASA, acetylsalicylic acid; BDS, budesonide; COX2-I, cyclooxygenase 2 inhibitor; CS, corticosteroids; DSCG, disodium cromoglycate; H1, H1 antihistamine; H2, H2 antihistamine; IFN, interferon; LT, leukotriene; NSAIDs, nonsteroidal antiinflammatory drugs; PPI, proton pump inhibitor; TKI, tyrosin-kinase inhibitor; VIT, venom immunotherapy.

^aTo be assessed in cases of spontaneous chronic urticaria.

^bPredominantly in cases with pruritus or lesions restricted to small skin areas.

^cProvided that tolerance is previously demonstrated.

^dIn cases with severe mast cell-mediator release symptoms such as hypotension or respiratory compromise, epinephrine must be administered as a first-line therapy.

^eIn selected cases, preferably through clinical trials or controlled observational studies.

^fIn cases with poor tolerance to VIT, consider omalizumab as an adjuvant.

Together with these discussed diagnostic criteria, a classification of MCAS also has been proposed, which divides MCAS into primary, secondary, or idiopathic (eTable 1).¹ According to this proposal, the study of the D816V *KIT* mutation and MC immunophenotyping should be performed systematically whenever criteria for MCAS are fulfilled, to confirm or rule out a primary MCAS. In contrast with MCAS presenting in patients with urticaria pigmentosa (UP), which would surely correspond to either cutaneous mastocytosis or systemic mastocytosis (SM), patients with systemic MC activation symptoms in the absence of UP cannot be ascribed to the clonal or nonclonal subgroups of MCAS without performing molecular and immunophenotypic studies. Preliminary unpublished data from the REMA show that the D816V *KIT* mutation as assessed by allele-specific oligonucleotide-quantitative polymerase chain reaction (ASO-qPCR) is detected in fluorescence-activated cell sorting (FACS)-purified bone marrow (BM) MCs but not in peripheral blood or unfractionated BM samples in approximately 20% of patients with indolent SM without skin lesions. These observations support that the *KIT* mutation is limited to a very small fraction of the hematopoiesis in some patients with clonal MCAS, and that BM studies using highly sensitive methods are mandatory for diagnosis purposes in such cases.^{3,4}

Because primary MCAS represents only a minority of all MCAS cases, the cost-effectiveness ratio of systematically performing a BM study in these patients would be high. For this reason, predictive models such as the REMA score or the National Institutes of Health

clinical activity score have been developed within the last decade to better select for those patients with high probability of having a clonal MC disorder who would then be candidates for BM studies.^{1,3} In patients with suspected MCAS without UP, we strongly recommend applying the REMA score as a first step. If the REMA score is ≥ 2 , a complete BM study is indicated. In patients with REMA score < 2 , we recommend searching for the *KIT* D816V mutant by ASO-qPCR in peripheral blood and, if positive, the study of the BM would be also indicated. Besides BM immunohistochemistry, aspirate samples for cytology, multiparameter flow-cytometry immunophenotyping, ASO-qPCR on unfractionated BM and FACS of BM MCs should also be obtained. When the D816V *KIT* mutation is not detected in BM by ASO-qPCR, then we recommend exploring the mutation by peptide nucleic acid (PNA)-mediated PCR clamping in FACS-purified BM MCs. If this molecular assay is also negative, sequencing of the whole *KIT* gene might be useful in selected cases.

Conclusions and Future Directions

Diagnosis of MCAS can be challenging for physicians who are not adequately experienced in mastocytosis and related disorders. It is strongly recommended to achieve a clear distinction between clonal and nonclonal MCAS, and, thus, patients with MCAS should be ideally referred to Reference Centers, which are characterized by multidisciplinary teams with broad clinical experience, availability of the

most cutting-edge technology for the diagnostic study of MC-related disorders, and ability to train patients, caregivers, and physicians.

Despite the major advances achieved in the last years in the diagnosis, classification, and treatment of MCAS, important issues such as the development of more specific and sensitive methods for the measurement of MC mediators, the relationship between MCAS and an increased copy numbers of *TPSAB1*,⁵ and the implementation of strategies for the study of the genetic background of nonclonal MCAS deserve further investigations.

Supplementary Data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.anai.2019.11.023>.

References

1. Valent P, Akin C, Bonadonna P, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. *J Allergy Clin Immunol Pract*. 2019; 7:1125–1133.
2. Weiler CR, Austen KF, Akin C, et al. AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management. *J Allergy Clin Immunol*. 2019;144:883–896.
3. Alvarez-Twose I, Gonzalez-de-Olano D, Sanchez-Munoz L, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *J Allergy Clin Immunol*. 2010;125:1269–1278.
4. Kristensen T, Vestergaard H, Moller MB. Improved detection of the KIT D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. *J Mol Diagn*. 2011;13:180–188.
5. Lyons JJ. Hereditary alpha tryptasemia: genotyping and associated clinical features. *Immunol Allergy Clin North Am*. 2018;38:483–495.

eTable 1Classification of Mast Cell Activation Syndromes^a

Genetics	Cause of MCA	Entities	Key diagnostic features
Clonal MCs	Primary	SM MMAS CM ^c	WHO major SM criterion and ≥ 1 minor criteria or ≥ 3 minor criteria without the major criterion are fulfilled Only 1 or 2 WHO minor SM criteria are fulfilled ^b
Non-clonal ^d MCs	Secondary	Allergy, cancer, autoimmune disorders, inflammatory diseases	Infiltration of skin by MCs in the absence of criteria for SM Well-established diseases or conditions able to induce MCA are diagnosed in the absence of clonal MCs
	Idiopathic	IA, CSU, IAE, idiopathic MCAS	Neither primary nor secondary causes of MCA are detected

Abbreviations: CSU, chronic spontaneous urticaria; CM, cutaneous mastocytosis; IA, idiopathic anaphylaxis; IAE, idiopathic angioedema; MC, mast cell; MCA, mast cell activation; MCAS, mast cell activation syndrome; MMAS, monoclonal mast cell activation syndrome; SM, systemic mastocytosis; WHO, World Health Organization.

^aAdapted from Valent et al.¹

^bOnly the minor diagnostic criteria that indicate MC clonality (ie, aberrant CD25 expression and codon 816 *KIT* mutations) are considered.

^cCM often presents without demonstrable clonal MCs but the skin MC infiltrate is widely accepted to be a clonal MC proliferation.

^dThe term “nonclonal” in MCAS refers to the absence of *KIT* mutations and their surrogate markers (ie, aberrant CD25 expression), but the potential existence of still undiscovered molecular defects in genes other than *KIT* cannot be ruled out.