

Frequency of clonal mast cell diseases among patients presenting with anaphylaxis: A prospective study in 178 patients from 5 tertiary centers in Spain

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Clinical Implications:

- Around 5% of all patients presenting with anaphylaxis in the absence of urticaria pigmentosa might have an underlying primary mast cell activation syndrome. The Red Española de Mastocytosis (“Spanish Network on Mastocytosis”) score represents a rather simple approach to select for patients without mastocytosis skin lesions who are candidates for further bone marrow analysis, with a high diagnostic efficiency.

TO THE EDITOR:

Mast cell activation syndromes (MCAS) encompass a heterogeneous group of disorders characterized by clinical symptoms secondary to the systemic effects of mediators released by mast cells (MCs) on their activation, including anaphylaxis. MCAS can be classified into 3 categories:^{1,2} (1) primary (monoclonal) MCAS, which includes symptomatic patients with systemic mastocytosis (SM) and those in whom clonal MCs and up to 2 minor SM criteria are found but SM cannot be diagnosed; (2) secondary MCAS; and (3) idiopathic MCAS. It is well established that anaphylaxis is a clinical manifestation of MCAS,³ and specific algorithms have been recently proposed to rule out an underlying primary MCAS in patients who present with anaphylaxis.⁴ However, the actual frequency of primary MCAS among patients presenting with anaphylaxis remains unknown. Patients with primary MCAS in the absence of skin lesions compatible with urticaria pigmentosa (UP) often present with anaphylaxis—either triggered by well-recognized antigens or without an identifiable cause; this clinical picture might contribute to masquerade the suspicion of an underlying primary MCAS.⁵ Currently, the diagnosis of primary MCAS requires demonstration of an underlying activating *KIT* mutation and/or an aberrant (eg, CD25+) immunophenotype in bone marrow

(BM) MCs, associated or not with additional World Health Organization diagnostic criteria for SM.⁶ Depending on the presence (vs absence) of BM aggregates and the number of minor diagnostic criteria for SM, 2 categories of primary (clonal) MCAS are recognized: indolent SM (ISM) without skin lesions (ISMs⁻) — also termed (isolated) BM mastocytosis (BMM) — and monoclonal MCAS (MMAS), respectively.⁴ Because the percentage of neoplastic MCs that infiltrate the BM in patients with primary MCAS is often low, high-sensitive diagnostic methods should be used in these cases, including next-generation multiparameter flow cytometry immunophenotyping and polymerase chain reaction (PCR)-based molecular assays including an allele-specific quantitative PCR assay (ASO-qPCR) in whole BM cells or a peptide nucleic acid-mediated PCR-clamping technique in purified BM MCs.⁶

BM analysis is currently required not only for the diagnosis of primary (clonal) MCAS, but also for clear cut distinction between clonal and nonclonal (eg, secondary and idiopathic) MCAS.⁴ This is particularly true because circulating MCs are usually not detectable in peripheral blood (PB) and in one third of all patients with *KIT* D816V+ ISMs⁻/BMM, this mutation can only be detected in BM.⁵ However, recent findings support that the efficacy in the detection of this mutation in PB could be improved by using the ASO-qPCR assay.⁷ Given the relatively high number of patients presenting with MCAS, systematic BM

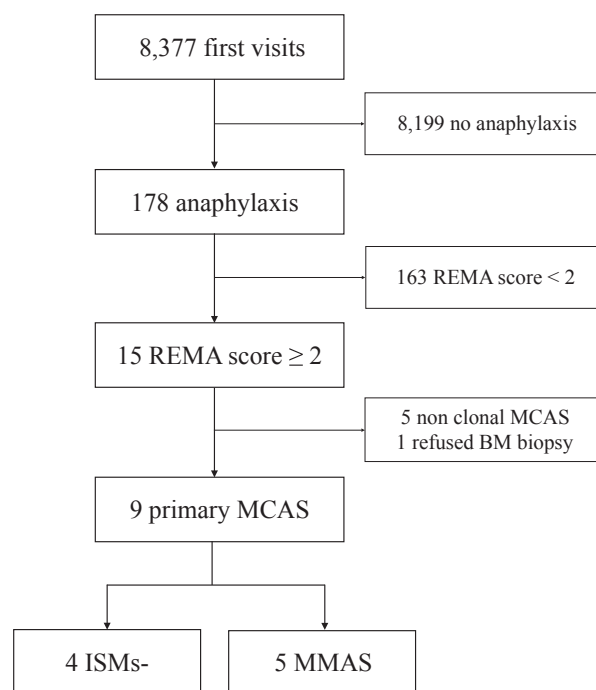


FIGURE 1. Flowchart of the patients. *BM*, Bone marrow; *ISMs⁻*, indolent systemic mastocytosis without skin involvement; *MCAS*, mast cell activation syndrome; *MMAS*, monoclonal mast cell activation syndrome; *REMA*, Red Española de Mastocytosis (Spanish Network on Mastocytosis).

TABLE 1. Demographic, clinical, and laboratory features of patients presenting with anaphylaxis grouped according to the REMA score

	REMA score < 2	REMA score ≥ 2	
	(n = 163)	Nonclonal MCAS (n = 5)	Primary MCAS (n = 9)
Male	64 (39)	1/4 (20)	7/2 (78)
Age (y)	43 (18-87)	56 (25-67)	59 (20-75)
Time to BM study (mo)	NA	16 (9-21)	13 (7-21)
No. of episodes	2 (1-25)	2 (1-10)	2 (1-4)
Total IgE (kU/L)	122.3 (3.0-3,630)	19.1 (12.0-3,000)	81.1 (10-226)
Baseline serum tryptase (mcg/L)	4.02 (1.1-23.1)	4.36 (2.1-16.6)	7.5 (2.6-19.1)
Etiology			
Food	57 (35)	0 (0)	1 (11.1)
Drugs	55 (33.7)	3 (60)	4 (44.4)
Unknown	20 (12.3)	0 (0)	0 (0)
Hymenoptera	12 (7.4)	1 (20)	2 (22.2)
<i>Anisakis simplex</i>	12 (7.4)	0 (0)	2 (22.2)
Mixture*	5 (3)	1 (20)	0 (0)
Others	2 (1.2)	0 (0)	0 (0)

BM, Bone marrow; MCAS, mast cell activation syndrome; NA, not applicable; REMA, Red Española de Mastocytosis ("Spanish Network on Mastocytosis").

Results expressed as number of cases/total cases studied (percentage) for categorical variables and median (range) for continuous variables.

*Patients presenting anaphylaxis with more than 1 trigger: food and drug (2 patients), hymenoptera sting and drug (1), hymenoptera sting and food (1), food and unknown trigger (1), and food, *Anisakis simplex*, and unknown trigger (1).

examination in all such cases is neither cost-effective nor feasible in routine clinical practice. To overcome these diagnostic challenges, the Red Española de Mastocytosis ("Spanish Network on Mastocytosis") (REMA) developed and validated a simple clinical score (ie, REMA score) that proved to be highly efficient to predict for primary MCAS (eg, ISMs[−] and MMAS) in patients with MC activation syndromes in the absence of UP referred to the Spanish reference center on mastocytosis.⁵ The proposed REMA score is based on easily accessible clinical and laboratory features, such as gender (score +1 for males vs score −1 for females), presence of cardiovascular (eg, dizziness and/or loss of consciousness, score +3), and other MC-mediator release associated symptoms (eg, presence vs absence of pruritus, hives and angioedema: score −2 vs score +1, respectively), and baseline serum tryptase (sBT) levels (eg, score +2 when sBT >25 µg/L vs score −1 when <15 µg/L) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Because according to the REMA, an overall score ≥2 is associated with a high probability of a primary MC disease (sensitivity: 0.92 and specificity: 0.81), such score could also be used to select among patients presenting with anaphylaxis, those who are candidates for a BM study, to confirm the diagnosis of primary (vs non-clonal) MCAS.

Here, we investigated the overall frequency of primary MCAS in the absence of UP, among patients attending the Department of Allergy from 5 tertiary Spanish hospitals for a period of 16 consecutive months.

From September 1, 2014, to December 31, 2015, a total of 178 unselected, consecutive patients who attended for the first time the Departments of Allergy of Hospital Universitario de Fuenlabrada (Madrid, Spain), Fundación Hospital de Alcorcón (Madrid, Spain), Hospital General de Segovia (Segovia, Spain), Hospital General Universitario Gregorio Marañón (Madrid, Spain), and Hospital Universitario Fundación Jiménez Díaz (Madrid, Spain) due to the history of anaphylaxis in the absence of UP were included in the study. According to Spanish national regulations, the study was approved by the Ethics Committee of

Hospital Universitario de Fuenlabrada as coordinating center, and it was conducted following the principles of the Declaration of Helsinki. The REMA score was applied to all patients fulfilling diagnostic criteria of anaphylaxis; from them, those who had an overall REMA score ≥2 were further referred to the Instituto de Estudios de Mastocitosis de Castilla-La Mancha (CLMast), the Spanish Reference Center of Mastocytosis for a complete BM study. The patients' flowchart and their main clinical features and laboratory findings are shown in Figure 1 and Table 1, respectively.

Overall, 178 of 8,377 consulting patients (2.1%) corresponded to patients suffering from anaphylaxis, a frequency similar to that reported in previous studies in Spain.⁸ Among these cases, 15 patients presenting with anaphylaxis had a REMA score ≥2 (8%); 14 of 15 cases underwent subsequent BM analyses (the remaining patient refused to undergo a diagnostic BM aspiration procedure). Nine patients were ultimately diagnosed with a primary MCAS on BM examination (64%), including 4 patients with ISMs[−] (28%) and 5 (36%) with MMAS (Table E2, available in this article's Online Repository at www.jaci-inpractice.org); the remaining 5 patients (36%) corresponded to nonclonal MCAS. Based on these findings, an overall frequency of 5% primary MCAS among patients with anaphylaxis is estimated, which would correspond to only 0.1% of all patients who consulted at the Departments of Allergy of the centers that participated in this study. As could be expected, a male predominance was observed in primary MCAS versus nonclonal MCAS cases (78% vs 20%, $P = .06$), in line with what has been repeatedly reported in the literature.^{3,5} In turn, when we investigated the distribution of different triggers for anaphylaxis among the cohort of 178 patients presenting with anaphylaxis, similar profiles to those reported in the literature were observed;⁸ thus, drugs and food were the most frequent elicitors in patients with REMA score <2 (35% and 33% of cases, respectively), followed by idiopathic anaphylaxis (12%), anaphylaxis due to hymenoptera sting (7%), *Anisakis simplex* (7%), mixed factors (3%), and others (1%). A slightly higher

frequency of anaphylaxis associated with hymenoptera sting was observed when analysis was restricted to the primary MCAS cases (22%); however, this frequency remains significantly lower than previously reported in ISMs⁺ and MMAS (53% to 66%), where insect sting/bite was the most common trigger of anaphylaxis.^{5,9} Such discrepancy might be explained by a potential patient selection bias in reference centers versus tertiary centers and/or to the small number of patients with primary MCAS analyzed here. Interestingly, most (6 of 9, 67%) patients with primary MCAS selected for BM analysis based on a high REMA score showed normal serum baseline tryptase levels (eg, <11.4 µg/L), highlighting the clinical relevance of this predictive model for the identification of patients with primary MCAS, particularly among cases presenting with anaphylaxis, associated with a low BM MC burden.

In summary, our results indicate that around 5% of all patients presenting with anaphylaxis in the absence of UP admitted at Allergy Departments in Spain have an underlying primary MCAS. The REMA score represents a rather simple approach to select for patients who are candidates for further BM analysis, with a high diagnostic efficiency.

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TABLE E1. Examples of application of the REMA score

Case no.	Score punctuation	Gender		Clinical symptoms			Baseline tryptase		Total score	Diagnosis*
		Male (+1)	Female (−1)	Absence of urticaria, pruritus, and angioedema (+1)	Urticaria, pruritus and/or angioedema (−2)	Presyncope or syncope (+3)	<15 ng/mL (−1)	>25 ng/mL (+2)		
Pt 1 [†]		Yes	No	Yes	No	Yes	Yes	No	4	MMAS
Pt 2 [†]		Yes	No	Yes	No	Yes	Yes	No	4	MMAS
Pt 3 [†]		Yes	No	Yes	No	Yes	Yes	No	4	ISM [−]
Pt 4 [†]		Yes	No	Yes	No	Yes	Yes	No	4	MMAS
Pt 5 [†]		Yes	No	Yes	No	Yes	Yes	No	4	MMAS
Pt 6 [†]		No	Yes	Yes	No	Yes	Yes	No	2	MMAS
Pt 7 [†]		Yes	No	No	Yes	Yes	No	No	2	ISM [−]
Pt 8 [†]		Yes	No	No	Yes	Yes	No	No	2	ISM [−]
Pt 9 [†]		No	Yes	No	No	Yes	No	No	2	ISM [−]
Pt 10 [†]		No	Yes	Yes	No	Yes	Yes	No	2	Nonclonal MCAS
Pt 11 [†]		No	Yes	Yes	No	Yes	Yes	No	2	Nonclonal MCAS
Pt 12 [†]		No	Yes	Yes	No	Yes	Yes	No	2	Nonclonal MCAS
Pt 13 [†]		No	Yes	Yes	No	Yes	Yes	No	2	Nonclonal MCAS
Pt 14 [†]		Yes	No	No	Yes	Yes	No	No	2	Nonclonal MCAS
Pt 15 [‡]		Yes	No	Yes	No	Yes	Yes	No	4	NK

ISM[−], Indolent systemic mastocytosis without skin involvement; MCAS, mast cell activation syndrome; MMAS, monoclonal mast cell activation syndrome; NK, not known; REMA, Red Española de Mastocytosis (“Spanish Network on Mastocytosis”).

Parenthetical values in the Gender, Clinical Symptoms, and Baseline Tryptase columns are the score punctuation.

*Diagnosis was reached after the performance of a bone marrow biopsy study.

†Demographic, clinical, and laboratory features of these patients presenting with anaphylaxis and a REMA score ≥ 2 are depicted in Table E2.

‡The patient refused to undergo a bone marrow study.

TABLE E2. Demographic, clinical, and laboratory features of patients presenting with anaphylaxis and a REMA score ≥ 2

Case no.	Sex	Age (y)	Time to BM study (mo)	No. of anaphylactic episodes	Trigger for anaphylaxis	Total IgE (kU/L)	Baseline serum tryptase (μ g/L)
Primary MCAS							
1	Male	71	14	1	Levofloxacin	35.6	2.6
2	Male	20	18	2	Local anesthetic	114.1	3.9
3	Male	50	11	1	Wasp	94.0	4.7
4	Male	64	21	2	Wasp	62.0	6
5	Male	68	13	2	Rocuronium	10.0	7.5
6	Female	75	9	2	Prawns	81.1	7.8
7	Male	59	10	4	<i>Anisakis simplex</i>	53.0	16.8
8	Male	54	18	2	<i>Anisakis simplex</i>	225.8	17.3
9	Female	50	7	1	Amoxicillin	101.2	19.1
Nonclonal MCAS							
10	Female	67	9	2	Diclofenac Wasp	3,000.0	2.1
11	Female	39	16	10	Wasp	13.2	2.4
12	Female	25	20	1	Dextromethorphan	19.1	4.3
13	Female	60	15	2	Amoxicillin-clavulanate	12.4	7.3
14	Male	56	21	2	Diclofenac	106.8	16.6

BM, Bone marrow; MCAS, mast cell activation syndrome; REMA, Red Española de Mastocytosis (“Spanish Network on Mastocytosis”).