

Clinical Communications

Mast cell activation diseases and chronic spontaneous urticaria: Common points and differences

Aurélie Madelon, MD, Isabelle Boccon-Gibod, MD, Catherine Mansard, MD, Alban Deroux, MD, Alexis Bocquet, MD, and Laurence Bouillet, MD, PhD

Clinical Implications

- Chronic spontaneous urticaria (CSU) with extracutaneous involvement (CSUe+) is not considered a mast cell activation syndrome (MCAS). Conversely, cutaneous signs are underestimated in MCAS. However, patients with CSUe+ and patients with MCAS present similar profiles: clinical, biological, and therapeutics. We suggest that CSUe+ can be classified as MCAS.

TO THE EDITOR:

Mast cell activation disorders (MCADs) are a family of heterogeneous pathologies related to mast cell accumulation or excessive degranulation.¹ The family contains 3 groups: (1) monoclonal MCAD including systemic mastocytosis (SM) and monoclonal mast cell activation syndrome (MMAS); (2) secondary MCAD including allergies and mast cell activation secondary to dysimmune or infectious diseases; and (3) non-clonal idiopathic MCAD (MCAS).^{2,3} The notion of MCAS is recent, and their classification has undergone several changes in the last few years. In 2010, Akin et al² proposed 4 diagnostic criteria for MCAS. High basal level of tryptase, or an increase during event, is considered a key criterion. The second key criterion is the improvement in symptoms with antihistamines. Chronic spontaneous urticaria (CSU) was at one time classified as a form of MCAD, whereas it no longer appears to be so in the latest classification published in 2017.¹ CSU is often associated with extracutaneous symptoms (CSUe+), which can improve with antihistamine.⁴ This corresponds to the criteria proposed by Akin et al² to define MCAS. It just misses the elevation of a mast cell activation biomarker including tryptase.

The objective of this study was to compare clinical and biological data of CSUe+ with the primary MCAD.

We retrospectively collected data on all patients diagnosed with SM, MMAS, MCAS, or CSUe+ who had been regularly followed since 2010 by the Department of Clinical Immunology of Grenoble Alpes University Hospital, France. A total of 105 patients were included in our study: 13 with SM, 25 with MMAS, 19 with MCAS, and 48 with CSUe+. Monoclonal mast cell disorders were diagnosed as follows: SM matched World Health Organization criteria, and MMAS fulfilled 1 or 2 SM minor criteria but no SM diagnosis. MCASs were matching all 4 criteria mentioned above, or responding to the criteria for idiopathic anaphylaxis, which was proposed as a subtype of MCAS by Akin. The latter can have normal tryptase level.² The mean

age of our cohort was 48 years (7-84 years). High proportions of patients had CSU: 30.8% of patients with SM, 28% of patients with MMAS, and 78.9% of patients with MCAS (Table I). The most common noncutaneous features were digestive disorders (50.5%) followed by neurological disorders (in particular headache) (20%), oculonasal disorders (20%), and respiratory symptoms (19%). Sixty percent to 80% of patients in the SM, MMAS, and MCAS groups had presented at least 1 anaphylactic reaction (Table I). Reactions to hymenoptera were predominant in the MMAS group (60%), to food and hymenoptera in the SM group (30.8%), and there were more reactions to medications or idiopathic cases in the MCAS group (36.8%).

Ninety-two percent of patients with SM had baseline serum tryptase levels above normal values ($>11.4 \mu\text{g/L}$) and 84% had levels exceeding $20 \mu\text{g/L}$; 42% of the MCAS group had high basal tryptase levels, of which 21% had levels exceeding $20 \mu\text{g/L}$. The MCAS median basal tryptase level was $6 \mu\text{g/L}$ compared with $4.1 \mu\text{g/L}$ for patients with CSUe+.

Most patients responded to antihistamine. Patients with CSUe+ required higher doses of antihistamines: 20% had 3 times the recommended dose per day. A total of 29 particularly severe cases were successfully treated with omalizumab including 2 patients with SM, 4 with MMAS, 5 with MCAS, and 18 with CSUe+.

The characteristics of our 105 patients with MCAD are similar to those of other cohorts reported in the literature.⁵ We may have higher rates of CSU in our monoclonal MCAD, but our center is a reference for both SM and CSU, maybe explaining a recruitment bias for these diseases. Furthermore, a previous study reported 2 cases of angioedema out of 15 indolent SM,⁶ and Alvarez-Twose et al⁷ described the absence of CSU in only 62.7% of their patients with SM. There is no significant difference between the MCAS and CSUe+ groups in terms of clinical cutaneous and extracutaneous manifestations. These 2 groups seemed clinically similar to each other and with the data in the literature^{4,5,7} (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Note that extracutaneous signs can appear before, after, or at the same time that urticaria and/or CSU is diagnosed.⁴

Anaphylaxis is a major prognostic factor of MCAD. Thirty-nine percent of patients with MCAD had experienced at least 1 anaphylactic reaction. This result is consistent with those of other studies (17%-89%). In MMAS, hymenoptera were responsible for most anaphylactic reactions, whereas in MCAS, medication was the most common trigger.^{5,7}

A biological criterion is necessary to confirm MCAD. The currently recognized mast cell activation biomarkers are serum tryptase concentrations before and during an attack, urinary histamine and urinary prostaglandin D2. In our cohort, we found that 40% of patients with MCAS showed elevated basal tryptase level, which is comparable with data from the literature (33%).⁶ Basal tryptase levels tend to be higher in monoclonal MCAD than in the nonmonoclonal forms. But, the sensitivity for clonality of basal tryptase is only 60%, and its specificity only 70%. So, an elevated tryptase level is neither a marker of clonality nor a marker of the absence of clonality when it is normal.

TABLE I. Clinical features

Feature	Total (105)	SM (13)	MMAS (25)	MCAS (19)	CSUe+ (48)
Mean age (y)	48.2 (7-84)	58.5 (31-84)	58.0 (7-79)	44.7 (7-70)	41.7 (8-78)
Women (%)	65	62	44	64	78
Median delay to diagnosis (y)	4 (1-11)	3 (0-6)	4 (2-20)	2 (0-12)	4 (1-10)
Autoimmune diseases	11 (10.6%)	2 (15.4%)	1 (4.2%)	1 (5.3%)	7 (14.9%)
Family history of SM	3 (2.9%)	0	0	1/19 (5.26%)	2 (2.25%)
Familial atopy	31 (30.1%)	1 (7.7%)	2 (8.3%)	8 (42.1%)	20 (42.5%)
CSU	74 (70%)	4 (30.8%)	7 (28%)	15 (78.9%)	48 (100%)
Isolated angioedema	13 (12.4%)	0	0	3 (15.8%)	10 (20.8%)
Flushes	4 (3.8%)	0	2 (8%)	2 (10.5%)	0
Joint pain	14 (13.3%)	2 (15.4%)	3 (12%)	1 (5.26%)	8 (16.7%)
Asthmatic bronchitis/asthma	20 (19%)	0	4 (16%)	3 (15.8%)	13 (27.1%)
Cardiovascular	18 (17.1%)	1 (7.7%)	6 (24%)	3 (15.8%)	8 (16.7%)
Digestive symptoms	53 (50.5%)	5 (38.5%)	7 (28%)	9 (47.4%)	32 (66.7%)
ENT symptoms	21 (20%)	1 (7.7%)	0	6 (31.6%)	14 (29.2%)
Headaches	17 (16.2%)	0	1 (4%)	4 (21.1%)	12 (25%)
Concentration or memory disorders	3 (2.9%)	0	1 (4%)	1 (5.3%)	1 (2.1%)
Fatigue	17 (16.2%)	4 (30.8%)	2 (8%)	4 (21.1%)	7 (14.6%)
Anaphylaxis	41 (39%)	8 (61.5%)	20 (80%)	13 (68.4%)	0

ENT symptoms, Ear, nose, and throat symptoms.

Cardiovascular symptoms were hypotension or tachycardia; digestive symptoms were diarrhea, abdominal pain, nausea, vomiting, or gastroesophageal reflux; and ENT symptoms were nasal stuffiness, pruritus, or conjunctivitis.

In the literature, tryptase level is significantly higher in patients with CSUe+ than in patients with CSU alone, but the increase remains below the threshold of 11.4 µg/L. This result suggests that the presence of systemic involvement in CSU could be related to mast cell activation. It should be noted that the level is not correlated with the number of extracutaneous symptoms⁴ and that elevated basal tryptase levels could be secondary to hereditary alaphtryptasemia, which was not checked in our patients.

Although an elevated tryptase level is one of the diagnostic criteria of MCAS, normal levels do not allow one to exclude this diagnosis.³ It therefore seems important to obtain tryptase levels during an attack, to regularly repeat measurements, or to determine urinary histamine or PGD2 concentrations, which unfortunately are not routinely done. Some authors suggested that the symptomatology of MCAS is due to an abnormal tissue response to a physiological level of mast cell mediators. Valent⁸ proposed to diagnose MCAS using only 2 of Akin et al's criteria. However, this may run the risk of overdiagnosis.

The response to treatments targeting mast cells and their mediators is an important part of the diagnosis. Picard et al⁹ found that one-third of patients with MCAS/MMAS had complete symptom resolution, one-third had a major response, and one-third had a minor response. In our study, we noted that patients with MCAS and CSUe+ appeared to require higher doses of antihistamines than those with SM or MMAS.

In conclusion, MCAS and CSUe+ have similar clinical and biological characteristics. MCAS has recently been recognized as a clinical entity, but its definition and diagnostic criteria are subject to controversy. The clinical signs are nonspecific, leading to a risk of overdiagnosis. It is important to obtain biological markers of mast cell activation, because basal tryptase level has some limitations. The diagnostic challenges should never delay

the start of antihistamines because they can dramatically improve the patients.

Acknowledgment

We thank Alison Foote, PhD (Grenoble Alpes University Hospital), for translating the manuscript.

Internal Medicine and Clinical Immunology Department, CREAK, Grenoble Alpes University Hospital, Grenoble, France

Conflicts of interest: The authors declare that they have no relevant conflicts of interest, financial or otherwise, with the work presented here.

Received for publication April 12, 2019; revised September 12, 2019; accepted for publication September 15, 2019.

Available online ■ ■

Corresponding author: Laurence Bouillet, MD, PhD, Grenoble Alpes University Hospital, Service de médecine interne, Centre Hospitalier Universitaire de Grenoble, CS 10217, Grenoble Cedex 09 38 043, France. E-mail: lbouillet@chu-grenoble.fr.

2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2019.09.016>

REFERENCES

1. Akin C. Mast cell activation syndromes. *J Allergy Clin Immunol* 2017;140:349-55.
2. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 2010;126:1099-1104.e4.
3. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012;157:215-25.
4. Doong JC, Chichester K, Oliver ET, Schwartz LB, Saini SS. Chronic idiopathic urticaria: systemic complaints and their relationship with disease and immune measures. *J Allergy Clin Immunol Pract* 2017;5:1314-8.
5. Álvarez-Twose I, Olano DG de, Sánchez-Muñoz L, Matito A, Esteban-López MI, Vega A, 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.e2.
6. Koterba A, Akin C. Differences in the clinical presentation of anaphylaxis in patients with indolent systemic mastocytosis versus idiopathic anaphylaxis [abstract]. *J Allergy Clin Immunol* 2008;121:S68.
 7. Alvarez-Twose I, González-de-Olano D, Sánchez-Muñoz L, Matito A, Jara-Acevedo M, Teodosio C, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. *Int Arch Allergy Immunol* 2012;157:275-80.
 8. Valent P. Mast cell activation syndromes: definition and classification. *Allergy* 2013;68:417-24.
 9. Picard M, Giavina-Bianchi P, Mezzano V, Castells M. Expanding spectrum of mast cell activation disorders: monoclonal and idiopathic mast cell activation syndromes. *Clin Ther* 2013;35:548-62.

ONLINE REPOSITORY

TABLE E1. Comparison with published data

MCAS	Present study 2019	Alvarez et al, ^{E1} 2012	Hamilton et al, ^{E2} 2011
Digestive symptoms	47%	13%-18%	94%
Headache	21%	4%	83%
Concentration or memory disorders	5%	—	67%
Asthmatic bronchitis/asthma	16%	50%	39%
ENT symptoms	32%	7%	39%
Anaphylaxis	68%	—	17%
CSUe+	Present study 2019	Doong et al, ^{E3} 2017	Sabroe et al, ^{E4} 1999
Joint pain	17%	55%	35%
Digestive symptoms	67%	26%	41%
Headache	25%	48%	69%
Asthmatic bronchitis/asthma	27%	30%	—
MMAS	Present study 2019	Alvarez et al, ^{E1} 2012	
Digestive symptoms	28%		18%
Headache	4%		0%
Asthmatic bronchitis/asthma	16%		64%
ENT symptoms	0%		0%
Anaphylaxis	80%		—

ENT symptoms, Ear, nose, and throat symptoms.

REFERENCES

- E1. Alvarez-Twose I, González-de-Olano D, Sánchez-Muñoz L, Matito A, Jara-Acevedo M, Teodosio C, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. *Int Arch Allergy Immunol* 2012;157:275-80.
- E2. Hamilton MJ, Hornick JL, Akin C, Castells MC, Greenberger NJ. Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations. *J Allergy Clin Immunol* 2011;128:147-152.e2.
- E3. Doong JC, Chichester K, Oliver ET, Schwartz LB, Saini SS. Chronic idiopathic urticaria: systemic complaints and their relationship with disease and immune measures. *J Allergy Clin Immunol Pract* 2017;5:1314-8.
- E4. Sabroe RA, Seed PT, Francis DM, Barr RM, Black AK, Greaves MW. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-FcεRI or anti-IgE autoantibodies. *J Am Acad Dermatol* 1999; 40:443-50.