Mast Cell Activation Syndrome: Tools for Diagnosis and Differential Diagnosis

Catherine R. Weiler, MD, PhD *Rochester, Minn*

The current consensus diagnostic criteria for mast cell activation syndrome(s) (MCAS[s]) were first established in 2012 and updated in 2019. This diagnosis has been attached to multiple medical conditions not intended as part of the diagnosis. In this article, the diagnostic criteria are reviewed and other diseases in the differential diagnosis outlined. The goal of this review is to provide a tool for evaluation of patients with conditions that can mimic MCAS. Furthermore, the potential role for hereditary alpha-tryptasemia in this group of disorders is discussed. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:498-506)

Key words: *Mast cell activation syndrome (MCAS); Mastocytosis; Tryptase; N-Methylhistamine; Prostaglandin; Leukotriene E_4; Diagnostic criteria of MCAS; Differential diagnosis of MCAS; Hereditary alpha-tryptasemia (HAT); Diagnostic algorithm for MCAS*

Mast cell activation syndromes (MCAS(s)) have been defined as a group of disorders in which patients experience symptoms precipitated by mast cell mediator release.[1-3] The first report in which the term MCAS was coined described a number of patients with symptoms and laboratory findings suggestive of mastocytosis. However, even though the markers of mast cell clonality were found, the diagnostic criteria for mastocytosis were not fulfilled.[4] The consensus diagnostic criteria for MCAS include 3 sets of requirements.[1,2] First, the patient should experience acute and recurrent symptoms secondary to mast cell mediator release. Two organ systems are affected simultaneously. Second, the acute episodes have to be associated with elevated mast cell mediator(s). The mediator specified in the reports is tryptase. Elevation of serum tryptase is defined as an increase of 20% + 2 ng/mL above basal levels. Finally, the symptoms should resolve with therapeutic agents directed at blocking mast cell mediator release or their effects.[1,2] The diagnostic criteria are summarized in Figure 1. A consensus diagnostic algorithm for differentiating different mast cell disorders has been outlined by Valent et al.[2] The term MCAS(s) in the diagnostic criteria was used as an umbrella for multiple types of mast cell disorders.

TYPES OF MCAS(s)

There are 2 types of MCAS(s), primary (clonal) and secondary (nonclonal) (Table I). Primary MCAS(s) have clonal markers such as *KIT* Asp816Val mutation, or aberrant expression of CD25 or CD2 on mast cells. The 2 primary groups of MCAS(s) are mastocytosis (cutaneous and systemic) and monoclonal MCAS. Patients with mastocytosis should fulfill the World Health Organization diagnostic criteria for this disorder.[5,6] There is 1 major criterion and 4 minor criteria. For a diagnosis of mastocytosis, the patient should have a minimum of 1 major and 1 minor criterion or 3 minor criteria (Table II). Patients with monoclonal MCAS fulfill 1 to 2 of the diagnostic criteria for mastocytosis and have evidence of mast cell clonality.

Nonclonal MCAS(s) consist of 2 types; the first is secondary mast cell activation via a known trigger such as IgE-mediated stimulation. The second is idiopathic in which the etiology of the factor(s) activating mast cells is not known (Table I).[2] Much of the current medical and lay literature uses the term MCAS synonymously with idiopathic MCAS and not with clonal or secondary MCAS(s).[1,2,8-17]

CONSENSUS DIAGNOSTIC CRITERIA FOR MCAS(s)

First criterion: symptoms

The symptoms of mast cell activation, according to the consensus criteria, are a direct result of mast cell mediator effects. The symptoms should be acute and recurrent; furthermore, at least 2 organ systems should be affected concurrently. The organ systems that can be affected by mast cell mediator release are cutaneous, gastrointestinal, cardiac, respiratory, and neuropsychiatric. Symptoms such as flushing and syncope are highly suggestive of mast cell activation.

Other disorders, however, need to be considered in the differential diagnosis. Obtaining a detailed medical history and performing an organ-specific physical examination are of critical importance. A number of other clinical conditions can present with acute and recurrent symptoms involving 2 or more organ systems. Symptoms of those conditions can mimic MCAS. A list of the potential symptoms in a number of those disorders is summarized in Table III. Other conditions, not mentioned in the table, have been extensively reviewed by Valent and Akin.[16] The allergist needs to work closely with the patient's primary physician and possibly other subspecialty physicians for the patient's best interest. It is worth noting that some of the conditions listed in Table III are much more common than mast cell disorders. Finally, one should consider symptoms related to

Division of Allergy, Mayo Clinic, Rochester, Minn

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication June 20, 2019; revised July 30, 2019; accepted for publication August 7, 2019.

Available online August 27, 2019.

Corresponding author: Catherine R. Weiler, MD, PhD, Division of Allergy, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: Weiler.catherine@mayo.edu.

2213-2198

https://doi.org/10.1016/j.jaip.2019.08.022

Abbreviations used
HAT- Hereditary alpha-tryptasemia
LTE_4- Leukotriene E_4
MCAS- Mast cell activation syndrome
N-MH- N-Methylhistamine
PG- Prostaglandin and its metabolites
POTS- Postural orthostatic hypotension with tachycardia syndrome

medication side effects and the possible presence of 2 concurrent conditions.

Second criterion: laboratory findings

To fulfill the diagnostic criteria of MCAS, patients should have an elevation of mast cell mediators at the time of development of symptoms. The only mast cell mediator with a specified increase in level is tryptase.[1,2,41] This has served the criteria well. Serum tryptase should be collected between 1 and 4 hours after a suspected mast cell activation spell. This level should be compared with baseline/basal tryptase levels. Basal tryptase levels should be collected at least 24 to 48 hours after a suspected mast cell activation event/spell. An elevation of the serum tryptase level by at least 20% plus 2 ng/mL is considered consistent with mast cell activation. The major drawback to this criterion is the availability of sample collection to perform the assay within this time period.

Other validated mast cell mediators include urinary N-methylhistamine (N-MH),[42-45] urinary prostaglandin (PG) metabolites,[45-49] and urinary leukotriene E_4 (LTE_4).[50] Studies have shown that during the symptoms of anaphylaxis the level of 9α-11β-prostaglandin F2 (9α-11β-PGF2) in urine was significantly higher than levels in healthy controls.[51] After anaphylaxis, 9α-11β-PGF2 increased during the 0- to 3-hour period. In contrast, the maximum increase of LTE_4 occurs during the 3- to 6-hour collection interval.[51] Urine LTE_4 is higher in those with anaphylaxis who developed severe hypotension in comparison with those without anaphylactic shock. Significant correlation is found between maximum LTE_4 and 9α-11β-PGF2 in patients with anaphylactic shock.[51] LTE_4 levels returned to normal 20 hours after the spell. The maximum increase was 5.5- to 2-fold above baseline. Furthermore, LTE_4 and N-MH levels rise in parallel during exercise-induced anaphylaxis.[52] 9α-11β-PGF2 is correlated with idiopathic MCAS, whereas N-MH is a better marker of clonal MCAS.[46]

Assays available for the 3 mediators used to require 24-hour urine collection. Current assays, however, are performed on a random urine sample. The best time frame for sample collection is around 3 hours after the suspected spell. The sample should be a fresh collection, with the bladder emptied at the time of the spell. An elevation by 30% above the upper end of the normal range can be, arbitrarily, considered consistent with an MC activation spell. To date, there are no available data for further validation of the level considered higher than baseline values. The assays are all commercially available at the Mayo Medical laboratory and are Clinical Laboratory Improvement Amendments (CLIA) certified. Once the physician orders the assays, from the Mayo Medical laboratories as a mail in specimen, the patient receives a kit by mail. The kit will always be available to the patient for collection of the urine sample and mailing it back to the laboratory after a suspected mast cell activation spell.

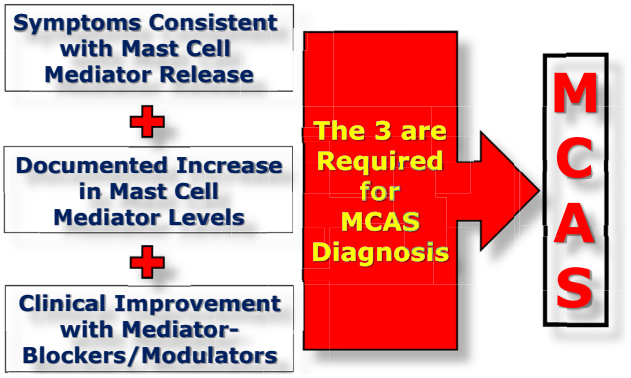

FIGURE 1. Summary of the current diagnostic criteria for MCAS(s). *MCAS*, Mast cell activation syndrome.

Instructions to the patient on collection and mailing the sample to the laboratory are included with the kit. The results will be sent to the ordering physician.

It is important to correlate mediator release with the occurrence of symptoms. The importance of this correlation is the elevation of tryptase and some of urinary mediators in other conditions (Table IV). Comprehensive and clinically relevant testing should be an integral part of the patient evaluation (Table IV).

Third criterion: therapeutic response

The third diagnostic criterion is response to therapy. It is clear from the above discussion that the therapeutic response to specific treatments is required to ensure that the diagnosis is correct. Therapies used in MCAS include medications that modify mediator production/stabilize mast cells, and/or medications that block or modify mediator effects or receptor binding.[15] Those medications include different classes and generations of antihistamines, leukotriene antagonists, sodium cromoglycate, 5-lipoxygenese inhibitors, and PG blockers. Injectable epinephrine is only needed for anaphylaxis. It is important to note that the treatment should be tailored to the patients' symptoms. If possible, therapy should target the elevated urinary mediators.[45] For example, patients with elevated PG metabolites and normal N-MH are more likely to benefit from aspirin, provided they are not aspirin allergic. Other comorbid conditions have to be treated independently and need to receive appropriate therapy. Patients with comorbid conditions should receive appropriate therapies as dictated by standard medical care. The goal is using the least number of beneficial medications at the lowest effective dose. The different therapeutic modalities for patients with MCAS have been reviewed in detail by Castells and Butterfield.[15]

Patients with clonal MCAS, not those with idiopathic MCAS, should be followed for the burden of the disease. Patients with clonal MCAS can be offered cytoreductive therapies on a case-by-case basis. Older cytoreductive modalities include interferon alpha,[56-65] hydroxyurea,[66] and cladribine.[66-71] Patients with aggressive systemic mastocytosis and those with mast cell leukemia could be placed on the newly approved therapy with midostaurin.[72-79] Avapritinib showed therapeutic promise in early studies, but it is not yet available for clinical use.[80-83] Patients with mastocytosis who do not have the *KIT*

TABLE I. Classification of MCAS(s)[5-7]

Primary (clonal) MCAS(s)	Cutaneous mastocytosis	Fulfills the WHO diagnostic criteria for cutaneous mastocytosis but not systemic mastocytosis
	Systemic mastocytosis	Fulfills WHO diagnostic criteria for systemic mastocytosis
	Monoclonal MCAS	Evidence for clonal mast cells identified; however, the WHO diagnostic criteria for mastocytosis are not fulfilled
Secondary (nonclonal) MCAS(s) and idiopathic MCAS	IgE-mediated mast cell activation	Identifiable trigger(s)
	Direct mast cell activation	Identifiable trigger(s)
	Idiopathic mast cell activation	No clearly identifiable etiology

MCAS, Mast cell activation syndrome; *WHO*, World Health Organization.

TABLE II. WHO diagnostic criteria for systemic mastocytosis

Criterion	Characteristic
Major criterion	Dense multifocal infiltrates of >15 mast cells in the bone marrow or another extracutaneous organ
Minor criteria	>25% of mast cells are atypical
	KIT mutation in codon 816 in the bone marrow or other extracutaneous organs
	Mast cells in the bone marrow or another extracutaneous organ express CD25 and/or CD2
	Baseline serum tryptase >20 ng/mL in the absence of a hematologic neoplasm*

WHO, World Health Organization.
For the diagnosis of mastocytosis, the patient should have at least 1 major and 1 minor criterion or 3 minor criteria.
*If the patient has another associated hematologic neoplasm, tryptase cannot be used as a diagnostic criterion.[5-7]

TABLE III. Differential diagnosis of symptoms resembling MCAS

	Symptoms	Derm			GI		CV			Rsp		NP
Organ system	Disorder	F[18-22]	U[23,24]	AE[24,25]	Da[26-30]	AP	S	HTN	TC	Ds	W	A/O
Cutaneous	Angioedema acquired	+	+	+	+	+	+		+	+	+	+
	Hereditary angioedema			+		+	+			+		+
Endocrine	Thyroid disorders	+	+	+	+	+		+	+			+
	Adrenal disorders	+	+		+	+	+		+			+
	Menopause	+	+			+			+			+
CV	Arrhythmias, myocardial infarction	+					+	+	+	+	+	
GI	Inflammatory bowel disease		+		+	+				+	+	
	Irritable bowel syndrome				+	+			+			+
Infectious diseases	Organ specific or systemic	+	+	+	+	+	+		+	+	+	+
Neurogenic	Stroke						+	+	+			+
Neoplasms	Hematologic myeloid	+	+	+	+							+
	Genitourinary		+	+	+	+						
	Medullary thyroid carcinoma	+			+				+			+
	Carcinoid	+			+	+					+	+
	Pheochromocytoma	+			+			+	+		+	+
	VIPoma or other secretory tumors	+			+	+						
Autoimmune disorders	Systemic or organ specific	+	+	+	+	+	+		+	+	+	+
	Vasculitidies	+	+	+	+	+	+	+	+	+	+	+
Medication	Serotonin syndrome[31]	+	+	+	+	+	+	+	+	+		+
	SSRI[31-34]	+				+			+			+
	Toxic or allergic reactions[35]	+	+	+	+	+	+	+	+	+	+	+
Toxins	Scombroid/histamine[36-40]	+	+	+	+	+				+	+	+
Psychiatric	Panic attacks	+			+	+	+		+	+	+	+

AE, Angioedema; *A/O*, anxiety and/or other neuropsychiatric symptoms; *AP*, abdominal pain/dyspepsia; *CV*, cardiovascular; *Da*, diarrhea; *Derm*, dermatologic; *Ds*, dyspnea; *F*, flushing; *GI*, gastrointestinal; *HTN*, hypertension; *MCAS*, mast cell activation syndrome; *NP*, neuropsychiatric; *Rsp*, respiratory; *S*, syncope; *SSRI*, serotonin reuptake inhibitors; *TC*, tachycardia and/or arrhythmia; *U*, urticaria; *VIPoma*, vasointestinal peptide (VIP) secreting tumor; *W*, wheezing.
"+": symptom combinations that can be potentially present in patients with the listed disorder.

Asp816Val mutation can benefit from imatinib mesylate.[66,84-93] Other agents, such as dasatinib, have not been successful.[94,95] Cytoreductive agents should not be used in patients with idiopathic MCAS. For a more detailed evaluation of the risks and benefits of the therapeutic agents, see the review by Castells and Butterfield.[15]

TABLE IV. Laboratory findings: disorders in the differential diagnosis

		Laboratory results									
Cell or system	**Disorder**	**Trypt**	**N-MH**	**PG**	**LTE4**	**5-HIAA**	**MTN**	**TSH**	**Cort**	**Cltn**	**G/VIP**
Mast cells	Clonal MCAS	+	+	+	+						
	Secondary MCAS	+	+	+	+						
	MCAS of other known etiology	+	+	+	+						
	Idiopathic MCAS	+	+	+	+						
Eosinophils	Hypereosinophilic syndrome(s)	+		+	+						
Cutaneous	Angioedema acquired	+						+			
Endocrine	Hyper- or hypothyroidism							+			
	Adrenal disorders								+		
GI	Inflammatory bowel disease[53-55]		+								
Renal	Insufficiency	+									
Respiratory	AERD				+						
Neoplasms	Immature myeloid progenitors	+									
	Genitourinary			+							
	Medullary thyroid carcinoma							+		+	
	Carcinoid					+					
	Pheochromocytoma						+				
	VIPoma or other secretory tumors										+
Medications	Proton pump inhibitors[35]										+
Toxins	Scombroid/histamine		+								

5-HIAA, 5-Hydroxyindole acetic acid; *AERD*, aspirin-exacerbated respiratory disease; *Cltn*, calcitonin; *Cort*, cortisol; *GI*, gastrointestinal; *G/VIP*, gastrin or vasointestinal peptide; *LTE4*, leukotriene E4; *MCAS*, mast cell activation syndrome; *MTN*, metanephrines and/or catecholamines; *N-MH*, N-methylhistamine; *PG*, prostaglandin metabolites; *Trypt*, serum tryptase; *TSH*, thyroid stimulating hormone; *VIPoma*, VIP secreting tumor.
"+": mediator combinations that can be abnormal in patients with the listed disorder.

TABLE V. Prevalence of disorders and symptoms associated with HAT

Organ system	**Condition**	**Percentages of patients with HAT who have the concomitant diagnosis***
Atopy	Environmental allergies or asthma	94
	Anaphylaxis	21-28
	Venom allergy	14-22
Gastrointestinal	Irritable bowel syndrome	49-58
	Gastroesophageal reflux disease	65-100
	Cramping abdominal pain with diarrhea	87
Cutaneous	Flushing and/or pruritus with or without urticarial	51-80
Skeletal	Congenital skeletal abnormalities	26-53
	Retained primary teeth	21-47
Chronic pain	Chronic arthralgia	45-73
	Headaches and generalized pain	47-73
Connective tissue disorders	Hypermobile joints	28-37
Dysautonomia	POTS	46
Neuropsychiatric diagnosis	Anxiety/depression	50
	Sleep disturbance	39-73

HAT, Hereditary alpha-tryptasemia; *POTS*, postural orthostatic hypotension with tachycardia syndrome.
*The percentage of symptoms and other conditions, henceforth the range, increase with higher alpha-tryptase gene copy number.[122-124,128]

CURRENT CONFUSION

A number of publications suggested that idiopathic MCAS, a misdiagnosis, is associated with a myriad of chronic medical conditions.[9,14,17,96-108] The conditions reported in association with idiopathic MCAS include neuropsychiatric disorders,[9,109] solid organ malignancies,[96,102,108,110] blood disorders,[98,101] nonspecific peripheral blood mutations,[111] and other rare conditions.[99] Within this confusion, the use of chemotherapeutic agents,[100] monoclonal antibodies,[103,105,107] and tyrosine kinase inhibitors[103,105,112] for idiopathic MCAS has been reported. The concern with this line of aggressive therapy is the lack of a clear diagnosis and lack of identified cellular targets.

Patients who are reported to have this misdiagnosis of "chronic" form of MCAS are reportedly disabled with multiple other chronic comorbidities.[113,114] In a number of case reports and published patient surveys, the diagnosis of

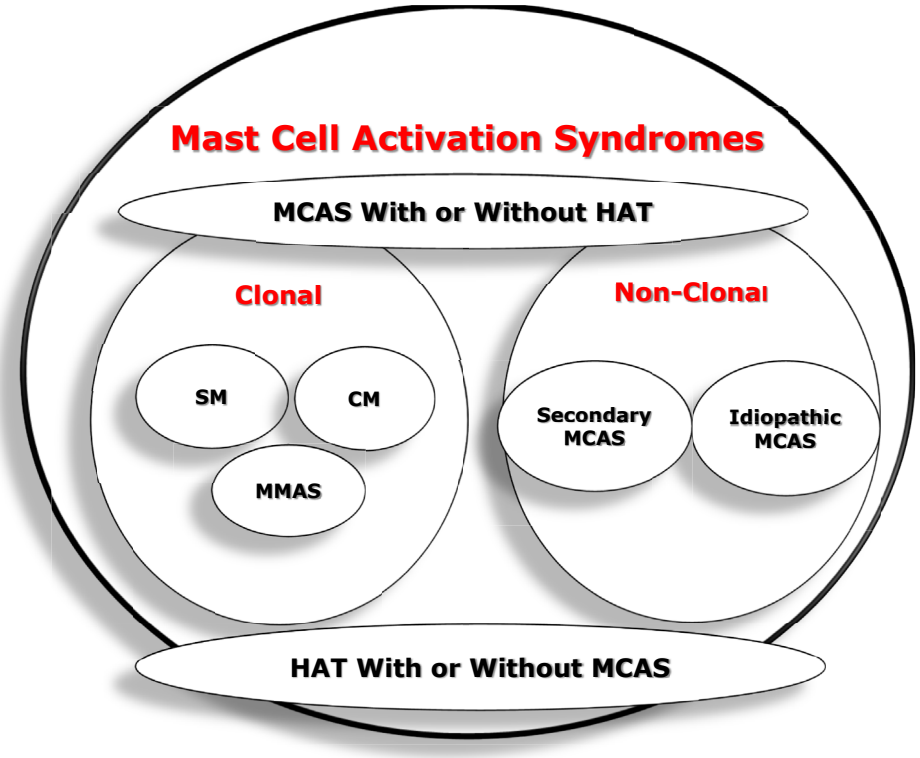

FIGURE 2. Types of different MCAS(s). *CM*, Cutaneous mastocytosis; *HAT*, hereditary alpha-tryptasemia; *MMAS*, monoclonal mast cell activation syndrome; *MCAS*, mast cell activation syndrome; *SM*, systemic mastocytosis.

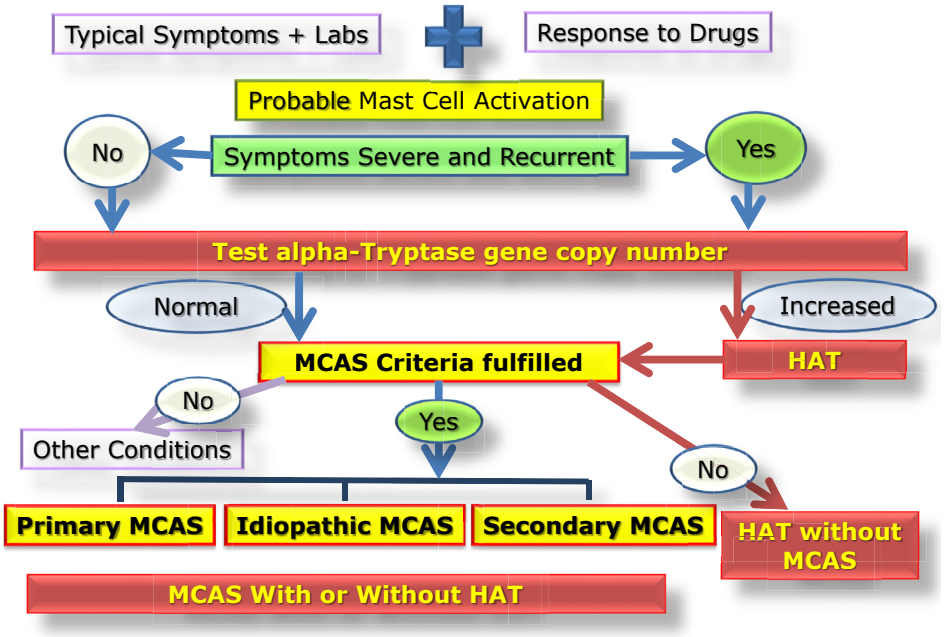

FIGURE 3. Proposed diagnostic algorithm for MCAS(s) in the setting of HAT. *HAT*, Hereditary alpha-tryptasemia; *MCAS*, mast cell activation syndrome.

idiopathic MCAS was associated with the comorbid diagnoses of postural orthostatic hypotension with tachycardia syndrome (POTS)[115-117] and/or joint hypermobility or Ehlers-Danlos syndrome,[113,114,116,118-120] among others. This misdiagnosis does not meet the consensus diagnostic criteria that specify the acuteness of symptoms. There is no evidence, to date, that implicates mast cell activation in any of those conditions.[121]

HEREDITARY ALPHA-TRYPTASEMIA

A new disorder in which patients and their family members have elevated serum tryptase was first described in 2014.[122] This disorder is inherited in an autosomal dominant fashion. Hereditary alpha-tryptasemia (HAT) is highly prevalent and affects an estimated 4% of the general population.[122,123] Patients with HAT are atopic and experience multiple atopic, connective tissue, gastrointestinal, and neuropsychiatric disorders.[122,123] The severity of the symptoms affecting patients with HAT is directly correlated with the level of serum tryptase. Further study of this patient population revealed duplication of the tryptase alpha gene.[123,124]

The tryptase gene locus, on chromosome 16p13.3, has 4 paralogous genes: *TPSG1*, *TPSB2*, *TPSAB1*, and *TPSD1*.[123,124] Serum tryptase is encoded by 2 of those genes that express the alpha- and beta-isoforms.[125-127] Beta-tryptase is encoded by *TPSB2*. *TPSAB1*, on the other hand, can encode either alpha- or beta-tryptase.[123,124] *TPSG1* encodes gamma-tryptase, which is membrane bound and not released in the circulation. *TPSD1* is not expressed. Patients with HAT have increased copy number of the *TPSAB1* gene encoding alpha-tryptase.[123,124] This results in an increase of levels of serum tryptase. Serum tryptase levels reflect the *TPSAB1* copy number. The higher the gene copy number, the higher the serum tryptase and the higher/worse the patient symptoms and comorbidities (Table V).[123,124]

Analysis of the tryptase gene copy number is currently available commercially. The company that performs the assay is "Gene by Gene, LTD." The details of ordering and mailing samples are available on the company's website. The order has to be placed by a physician and requires a buccal swab. The cost of the assay is $169 and might not be covered by the patient's insurance.

HAT AND MCAS(s)

The clinical findings in patients with HAT overlap with those reported in the "chronic" form of MCAS(s). Many of the symptoms and conditions identified in patients with HAT[122-124] have been associated with "chronic" MCAS.[128] Patients with HAT have a high prevalence of environmental allergies, asthma, anaphylaxis, urticaria, flushing, abdominal pain, and diarrhea. Furthermore, they can have connective tissue disorders, hypermobile joint disorders, neuropsychiatric diagnoses, chronic musculoskeletal pain, and POTS (Table V). The etiology of this symptom complex remains to be known. At this point in time, the only other gene identified in close proximity to tryptase is CACNA1H.[129] CACNA1H can be coinherited with the tryptase genes, but the clinical significance of this coinheritance is yet to be identified.[129]

HAT is not part of the definition of MCAS(s). It is, therefore, clinically beneficial to consider HAT in the differential diagnosis of patients with chronic symptoms. Not all patients with unusual symptoms have HAT. However, all patients with those symptoms want a diagnosis. Even though current treatments are directed at each associated condition, a diagnosis is what patients are seeking. Information regarding the commercial availability of the assay is discussed in this article.

HAT AND MCAS, MORE QUESTIONS

The identification of HAT puts forth more questions than answers regarding MCAS(s).[128] The percentage of patients with clonal and idiopathic MCAS(s) who have HAT, and vice versa, is unknown. Are all the patients with idiopathic MCAS actually patients with HAT? Is serum tryptase responsible for the symptoms? Are there multiple types of idiopathic MCAS(s)? Is HAT a clonal mast cell disorder? Is there linkage disequilibrium between the *TPSAB1* and other genes or gene promoters/inhibitors resulting in those acute and chronic symptoms and syndromes? Should HAT gene testing be part of the diagnostic algorithm?

CONCLUSIONS

Despite well-delineated criteria for diagnosis of clonal, secondary, and idiopathic MCAS, the field is in a state of flux. At this point, adhering to the diagnostic criteria and therapeutic recommendations is in the best benefit of patients (Figure 2). Each patient should undergo an evaluation of the disorders in the differential diagnosis. The role HAT should or does play in the diagnosis is evolving. A proposed diagnostic algorithm, modified from the international consensus diagnostic criteria for MCAS,[2] is outlined in Figure 3. It is clear, at this juncture, that further research is needed to address the questions posed above.

REFERENCES

1. 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.
2. Valent P, Akin C, Bonadonna P, Hartmann K, Brockow K, Niedoszytko M, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. J Allergy Clin Immunol Pract 2019;7:1125-11233.e1.
3. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol 2010;126:1099-1104.e4.
4. Akin C, Scott LM, Kocabas CN, Kushnir-Sukhov N, Brittain E, Noel P, et al. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with "idiopathic" anaphylaxis. Blood 2007;110:2331-3.
5. Valent P, Akin C, Metcalfe DD, Mastocytosis. 2016 updated WHO classification and novel emerging treatment concepts. Blood 2017;129:1420-7.
6. Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. Am J Hematol 2019;94:363-77.
7. Valent P, Akin C, Bonadonna P, Hartmann K, Broesby-Olsen S, Brockow K, et al. Mast cell activation syndrome: importance of consensus criteria and call for research. J Allergy Clin Immunol 2018;142:1008-10.
8. 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.
9. Afrin LB, Self S, Menk J, Lazarchick J. Characterization of mast cell activation syndrome. Am J Med Sci 2017;353:207-15.
10. Kramer ON, Barkoff MS, Hernandez C. Mast cell activation syndrome. Skinmed 2017;15:477-9.
11. Frieri M. Mast cell activation syndrome. Clin Rev Allergy Immunol 2018;54:353-65.
12. Kesterson K, Nahmias Z, Brestoff JR, Bodet ND, Kau A, Kim BS. Generalized pruritus relieved by NSAIDs in the setting of mast cell activation syndrome. J Allergy Clin Immunol Pract 2018;6:2130-1.
13. Kumaraswami S, Farkas G. Management of a parturient with mast cell activation syndrome: an anesthesiologist's experience. Case Rep Anesthesiol 2018;2018:8920921.
14. Afrin LB. Nonhistaminergic idiopathic angioedema may be a presentation of mast cell activation syndrome. J Investig Allergol Clin Immunol 2013;23:212.
15. Castells M, Butterfield J. Mast cell activation syndrome and mastocytosis: initial treatment options and long-term management. J Allergy Clin Immunol Pract 2019;7:1097-106.
16. Valent P, Akin C. Doctor, I think I am suffering from MCAS: differential diagnosis and separating facts from fiction. J Allergy Clin Immunol Pract 2019;7:1109-14.
17. Afrin LB. Never bet against occam: mast cell activation disease and the modern epidemics of chronic illness and medical complexity. 1st ed. Bethesda, MD: Sisters Media, LLC; 2016.

18. Rastogi V, Singh D, Mazza JJ, Parajuli D, Yale SH. Flushing disorders associated with gastrointestinal symptoms: part 1, neuroendocrine tumors, mast cell disorders and hyperbasophila. Clin Med Res 2018;16:16-28.
19. Rastogi V, Singh D, Mazza JJ, Parajuli D, Yale SH. Flushing disorders associated with gastrointestinal symptoms: part 2, systemic miscellaneous conditions. Clin Med Res 2018;16:29-36.
20. Sadeghian A, Rouhana H, Oswald-Stumpf B, Boh E. Etiologies and management of cutaneous flushing: nonmalignant causes. J Am Acad Dermatol 2017;77:391-402.
21. Sadeghian A, Rouhana H, Oswald-Stumpf B, Boh E. Etiologies and management of cutaneous flushing: malignant causes. J Am Acad Dermatol 2017;77:405-14.
22. Sood A, Arora R. Mechanisms of flushing due to niacin and abolition of these effects. J Clin Hypertens (Greenwich) 2009;11:685-9.
23. Westby EP, Lynde C, Sussman G. Chronic urticaria: following practice guidelines. Skin Therapy Lett 2018;23:1-4.
24. Radonjic-Hoesli S, Hofmeier KS, Micaletto S, Schmid-Grendelmeier P, Bircher A, Simon D. Urticaria and angioedema: an update on classification and pathogenesis. Clin Rev Allergy Immunol 2018;54:88-101.
25. Nedelea I, Deleanu D. Isolated angioedema: an overview of clinical features and etiology. Exp Ther Med 2019;17:1068-72.
26. Fabian E, Kump P, Krejs GJ. Diarrhea caused by circulating agents. Gastroenterol Clin North Am 2012;41:603-10.
27. Ikuta S, Yasui C, Kawanaka M, Aihara T, Yoshie H, Yanagi H, et al. Watery diarrhea, hypokalemia and achlorhydria syndrome due to an adrenal pheochromocytoma. World J Gastroenterol 2007;13:4649-52.
28. Pasieka JL, Hershfield N. Pancreatic polypeptide hyperplasia causing watery diarrhea syndrome: a case report. Can J Surg 1999;42:55-8.
29. Jensen RT. Overview of chronic diarrhea caused by functional neuroendocrine neoplasms. Semin Gastrointest Dis 1999;10:156-72.
30. Harris AG, O'Dorisio TM, Woltering EA, Anthony LB, Burton FR, Geller RB, et al. Consensus statement: octreotide dose titration in secretory diarrhea. Diarrhea Management Consensus Development Panel. Dig Dis Sci 1995;40:1464-73.
31. Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust 2007;187:361-5.
32. Ezzo DC, Patel PN. Facial flushing associated with duloxetine use. Am J Health Syst Pharm 2007;64:495-6.
33. Grenha J, Garrido A, Brito H, Oliveira MJ, Santos F. Serotonin syndrome after sertraline overdose in a child: a case report. Case Rep Pediatr 2013;2013:897902.
34. Velez LI, Shepherd G, Roth BA, Benitez FL. Serotonin syndrome with elevated paroxetine concentrations. Ann Pharmacother 2004;38:269-72.
35. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. Dig Dis Sci 2011;56:931-50.
36. Chomchai S, Chomchai C. Histamine poisoning from insect consumption: an outbreak investigation from Thailand. Clin Toxicol (Phila) 2018;56:126-31.
37. Centers for Disease Control and Prevention (CDC). Scombroid fish poisoning associated with tuna steaks–Louisiana and Tennessee, 2006. MMWR Morb Mortal Wkly Rep 2007;56:817-9.
38. Wu SF, Chen W. An outbreak of scombroid fish poisoning in a kindergarten. Acta Paediatr Taiwan 2003;44:297-9.
39. Wilson BJ, Musto RJ, Ghali WA. A case of histamine fish poisoning in a young atopic woman. J Gen Intern Med 2012;27:878-81.
40. Hall M. Something fishy: six patients with an unusual cause of food poisoning! Emerg Med (Fremantle) 2003;15:293-5.
41. Baretto RL, Beck S, Heslegrave J, Melchior C, Mohamed O, Ekbote A, et al. Validation of international consensus equation for acute serum total tryptase in mast cell activation: a perioperative perspective. Allergy 2017;72:2031-4.
42. Van Gysel D, Oranje AP, Vermeiden I, de Lijster de Raadt J, Mulder PG, van Toorenenbergen AW. Value of urinary N-methylhistamine measurements in childhood mastocytosis. J Am Acad Dermatol 1996;35:556-8.
43. Oranje AP, Mulder PG, Heide R, Tank B, Riezebos P, van Toorenenbergen AW. Urinary N-methylhistamine as an indicator of bone marrow involvement in mastocytosis. Clin Exp Dermatol 2002;27:502-6.
44. van Toorenenbergen AW, Oranje AP. Comparison of serum tryptase and urine N-methylhistamine in patients with suspected mastocytosis. Clin Chim Acta 2005;359:72-7.
45. Butterfield JH, Ravi A, Pongdee T. Mast cell mediators of significance in clinical practice in mastocytosis. Immunol Allergy Clin North Am 2018;38:397-410.
46. Ravi A, Butterfield J, Weiler CR. Mast cell activation syndrome: improved identification by combined determinations of serum tryptase and 24-hour urine 11beta-prostaglandin2alpha. J Allergy Clin Immunol Pract 2014;2:775-8.
47. Cho C, Nguyen A, Bryant KJ, O'Neill SG, McNeil HP. Prostaglandin D2 metabolites as a biomarker of in vivo mast cell activation in systemic mastocytosis and rheumatoid arthritis. Immun Inflamm Dis 2016;4:64-9.
48. Butterfield JH, Kao PC, Klee GC, Yocum MW. Aspirin idiosyncrasy in systemic mast cell disease: a new look at mediator release during aspirin desensitization. Mayo Clin Proc 1995;70:481-7.
49. Divekar R, Butterfield J. Urinary 11beta-PGF2alpha and N-methyl histamine correlate with bone marrow biopsy findings in mast cell disorders. Allergy 2015;70:1230-8.
50. Butterfield JH. Increased leukotriene E4 excretion in systemic mastocytosis. Prostaglandins Other Lipid Mediat 2010;92:73-6.
51. Ono E, Taniguchi M, Mita H, Fukutomi Y, Higashi N, Miyazaki E, et al. Increased production of cysteinyl leukotrienes and prostaglandin D2 during human anaphylaxis. Clin Exp Allergy 2009;39:72-80.
52. Denzlinger C, Haberl C, Wilmanns W. Cysteinyl leukotriene production in anaphylactic reactions. Int Arch Allergy Immunol 1995;108:158-64.
53. Bischoff SC, Grabowsky J, Manns MP. Quantification of inflammatory mediators in stool samples of patients with inflammatory bowel disorders and controls. Dig Dis Sci 1997;42:394-403.
54. Weidenhiller M, Raithel M, Winterkamp S, Otte P, Stolper J, Hahn EG. Methylhistamine in Crohn's disease (CD): increased production and elevated urine excretion correlates with disease activity. Inflamm Res 2000;49(Suppl 1):S35-6.
55. Winterkamp S, Weidenhiller M, Otte P, Stolper J, Schwab D, Hahn EG, et al. Urinary excretion of N-methylhistamine as a marker of disease activity in inflammatory bowel disease. Am J Gastroenterol 2002;97:3071-7.
56. Kluin-Nelemans HC, Jansen JH, Breukelman H, Wolthers BG, Kluin PM, Kroon HM, et al. Response to interferon alfa-2b in a patient with systemic mastocytosis. N Engl J Med 1992;326:619-23.
57. Czarnetzki BM, Algermissen B, Jeep S, Haas N, Nurnberg W, Muller K, et al. Interferon treatment of patients with chronic urticaria and mastocytosis. J Am Acad Dermatol 1994;30:500-1.
58. Harrison BD, Ashford RA, Hatton CS. Systemic mastocytosis—a case treated with interferon alpha and radiotherapy. Clin Lab Haematol 1994;16:291-4.
59. Pulik M, Lionnet F, Petit A, Genet P, Gaulier A. Long-term response to interferon-alpha in a patient with systemic mastocytosis and chronic myelomonocytic leukemia. Am J Hematol 1994;47:66.
60. Hubner C, Wedding U, Strater J, Limberg B, Stremmel W. Clinical stable systemic mastocytosis with interferon alpha-2b therapy. J Intern Med 1997;241:529-33.
61. Butterfield JH. Response of severe systemic mastocytosis to interferon alpha. Br J Dermatol 1998;138:489-95.
62. Casassus P, Caillat-Vigneron N, Martin A, Simon J, Gallais V, Beaudry P, et al. Treatment of adult systemic mastocytosis with interferon-alpha: results of a multicentre phase II trial on 20 patients. Br J Haematol 2002;119:1090-7.
63. Simon J, Lortholary O, Caillat-Vigneron N, Raphael M, Martin A, Briere J, et al. Interest of interferon alpha in systemic mastocytosis. The French experience and review of the literature. Pathol Biol (Paris) 2004;52:294-9.
64. Yoshida C, Takeuchi M, Tsuchiyama J, Sadahira Y. Successful treatment of KIT D816V-positive, imatinib-resistant systemic mastocytosis with interferon-alpha. Intern Med 2009;48:1973-8.
65. Bjerrum OW. Interferon-alpha treatment in systemic mastocytosis. Curr Drug Targets 2011;12:433-6.
66. Lim KH, Pardanani A, Butterfield JH, Li CY, Tefferi A. Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. Am J Hematol 2009;84:790-4.
67. Kluin-Nelemans HC, Oldhoff JM, Van Doormaal JJ, Van't Wout JW, Verhoef G, Gerrits WB, et al. Cladribine therapy for systemic mastocytosis. Blood 2003;102:4270-6.
68. Radojkovic M, Ristic S, Colovic N, Terzic T, Colovic M. Response to cladribine in patient with systemic mastocytosis. Vojnosanit Pregl 2011;68:444-6.
69. Bennett M, Chubar Y. Response of urticaria pigmentosa to cladribine in a patient with systemic mastocytosis. Br J Haematol 2013;160:420.
70. Akin C. Cladribine for mastocytosis: benefits and risks. Blood 2015;126:931-2.
71. Barete S, Lortholary O, Damaj G, Hirsch I, Chandesris MO, Elie C, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Blood 2015;126:1009-16. quiz 50.
72. Chandesris MO, Damaj G, Canioni D, Brouzes C, Lhermitte L, Hanssens K, et al. Midostaurin in advanced systemic mastocytosis. N Engl J Med 2016;374:2605-7.
73. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016;374:2530-41.

74. Gotlib J. A molecular roadmap for midostaurin in mastocytosis. Blood 2017; 130:98-100.
75. Jawhar M, Schwaab J, Naumann N, Horny HP, Sotlar K, Haferlach T, et al. Response and progression on midostaurin in advanced systemic mastocytosis: KIT D816V and other molecular markers. Blood 2017;130:137-45.
76. DeAngelo DJ, George TI, Linder A, Langford C, Perkins C, Ma J, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. Leukemia 2018;32:470-8.
77. Kasamon YL, Ko CW, Subramaniam S, Ma L, Yang Y, Nie L, et al. FDA approval summary: midostaurin for the treatment of advanced systemic mastocytosis. Oncologist 2018;23:1511-9.
78. van Anrooij B, Oude Elberink JNG, Span LFR, de Monchy JGR, Rosati S, Mulder AB, et al. Midostaurin in patients with indolent systemic mastocytosis: an open-label phase 2 trial. J Allergy Clin Immunol 2018;142:1006-1008.e7.
79. Martynova A, Nael A, O Neill C, Ramsingh G, Merchant A, Yaghmour B, et al. Aggressive systemic mastocytosis: midostaurin is safe, feasible and associated with durable response post-haploidentical allogeneic stem cell transplant. Br J Haematol 2019;186:e139-41.
80. Rapid responses to avapritinib (BLU-285) in mastocytosis. Cancer Discov 2018;8:133.
81. Gebreyohannes YK, Wozniak A, Zhai ME, Wellens J, Cornillie J, Vanleeuw U, et al. Robust activity of avapritinib, potent and highly selective inhibitor of mutated KIT, in patient-derived xenograft models of gastrointestinal stromal tumors. Clin Cancer Res 2019;25:609-18.
82. Lubke J, Naumann N, Kluger S, Schwaab J, Metzgeroth G, Evans E, et al. Inhibitory effects of midostaurin and avapritinib on myeloid progenitors derived from patients with KIT D816V positive advanced systemic mastocytosis. Leukemia 2019;33:1195-205.
83. Wu CP, Lusvarghi S, Wang JC, Hsiao SH, Huang YH, Hung TH, et al. Avapritinib, a selective inhibitor of KIT and PDGFRalpha reverses ABCB1 and ABCG2-mediated multidrug resistance in cancer cell lines. Mol Pharm 2019;16:3040-52.
84. Akin C, Fumo G, Yavuz AS, Lipsky PE, Neckers L, Metcalfe DD. A novel form of mastocytosis associated with a transmembrane c-kit mutation and response to imatinib. Blood 2004;103:3222-5.
85. Musto P, Falcone A, Sanpaolo G, Bodenizza C, Carella AM. Inefficacy of imatinib-mesylate in sporadic, aggressive systemic mastocytosis. Leuk Res 2004;28:421-2.
86. Droogendijk HJ, Kluin-Nelemans HJ, van Doormaal JJ, Oranje AP, van de Loosdrecht AA, van Daele PL. Imatinib mesylate in the treatment of systemic mastocytosis: a phase II trial. Cancer 2006;107:345-51.
87. Zhang LY, Smith ML, Schultheis B, Fitzgibbon J, Lister TA, Melo JV, et al. A novel K509I mutation of KIT identified in familial mastocytosis-in vitro and in vivo responsiveness to imatinib therapy. Leuk Res 2006;30: 373-8.
88. Dalal BI, Horsman DE, Bruyere H, Forrest DL. Imatinib mesylate responsiveness in aggressive systemic mastocytosis: novel association with a platelet derived growth factor receptor beta mutation. Am J Hematol 2007; 82:77-9.
89. Gollard RP, Ruemmler-Fish C, Garcia D. Systemic mastocytosis: documented pathologic response to imatinib. Eur J Haematol 2007;79:367-8.
90. Nakagomi N, Hirota S. Juxtamembrane-type c-kit gene mutation found in aggressive systemic mastocytosis induces imatinib-resistant constitutive KIT activation. Lab Invest 2007;87:365-71.
91. Valent P, Cerny-Reiterer S, Hoermann G, Sperr WR, Mullauer L, Mannhalter C, et al. Long-lasting complete response to imatinib in a patient with systemic mastocytosis exhibiting wild type KIT. Am J Blood Res 2014;4: 93-100.
92. Alvarez-Twose I, Matito A, Morgado JM, Sanchez-Munoz L, Jara-Acevedo M, Garcia-Montero A, et al. Imatinib in systemic mastocytosis: a phase IV clinical trial in patients lacking exon 17 KIT mutations and review of the literature. Oncotarget 2017;8:68950-63.
93. Broderick V, Waghorn K, Langabeer SE, Jeffers M, Cross NCP, Hayden PJ. Molecular response to imatinib in KIT F522C-mutated systemic mastocytosis. Leuk Res 2019;77:28-9.
94. Purtill D, Cooney J, Sinniah R, Carnley B, Cull G, Augustson B, et al. Dasatinib therapy for systemic mastocytosis: four cases. Eur J Haematol 2008; 80:456-8.
95. Gleixner KV, Mayerhofer M, Cerny-Reiterer S, Hormann G, Rix U, Bennett KL, et al. KIT-D816V-independent oncogenic signaling in neoplastic cells in systemic mastocytosis: role of Lyn and Btk activation and disruption by dasatinib and bosutinib. Blood 2011;118:1885-98.
96. Afrin LB. Polycythemia from mast cell activation syndrome: lessons learned. Am J Med Sci 2011;342:44-9.
97. Afrin LB. Burning mouth syndrome and mast cell activation disorder. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:465-72.
98. Afrin LB. Mast cell activation syndrome masquerading as agranulocytosis. Mil Med 2012;177:113-7.
99. Afrin LB. Sclerosing mediastinitis and mast cell activation syndrome. Pathol Res Pract 2012;208:181-5.
100. Afrin LB. Utility of hydroxyurea in mast cell activation syndrome. Exp Hematol Oncol 2013;2:28.
101. Afrin LB. Mast cell activation syndrome as a significant comorbidity in sickle cell disease. Am J Med Sci 2014;348:460-4.
102. Afrin LB, Spruill LS, Schabel SI, Young-Pierce JL. Improved metastatic uterine papillary serous cancer outcome with treatment of mast cell activation syndrome. Oncology (Williston Park) 2014;28:129-131, 34.
103. Afrin LB, Cichocki FM, Patel K, Molderings GJ. Successful treatment of mast cell activation syndrome with sunitinib. Eur J Haematol 2015;95:595-7.
104. Randall N, Courville EL, Baughn L, Afrin L, Ustun C. Bosutinib, a Lyn/Btk inhibiting tyrosine kinase inhibitor, is ineffective in advanced systemic mastocytosis. Am J Hematol 2015;90:E74.
105. Afrin LB, Fox RW, Zito SL, Choe L, Glover SC. Successful targeted treatment of mast cell activation syndrome with tofacitinib. Eur J Haematol 2017;99: 190-3.
106. Lortholary O, Chandesris MO, Bulai Livideanu C, Paul C, Guillet G, Jassem E, et al. Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomised, placebo-controlled, phase 3 study. Lancet 2017;389:612-20.
107. Molderings GJ, Afrin LB, Hertfelder HJ, Brettner S. Case report: treatment of systemic mastocytosis with sunitinib. F1000Res 2017;6:2182.
108. Molderings GJ, Zienkiewicz T, Homann J, Menzen M, Afrin LB. Risk of solid cancer in patients with mast cell activation syndrome: results from Germany and USA. F1000Res 2017;6:1889.
109. Haenisch B, Molderings GJ. White matter abnormalities are also repeatedly present in patients with systemic mast cell activation syndrome. Transl Psychiatry 2018;8:95.
110. Molderings GJ, Knuchel-Clarke R, Hertfelder HJ, Kuhl C. Mast cell activation syndrome mimicking breast cancer: case report with pathophysiologic considerations. Clin Breast Cancer 2018;18:e271-6.
111. Altmuller J, Haenisch B, Kawalia A, Menzen M, Nothen MM, Fier H, et al. Mutational profiling in the peripheral blood leukocytes of patients with systemic mast cell activation syndrome using next-generation sequencing. Immunogenetics 2017;69:359-69.
112. Malik F, Ali N, Jafri SIM, Ghani A, Hamid M, Boigon M, et al. Continuous diphenhydramine infusion and imatinib for KIT-D816V-negative mast cell activation syndrome: a case report. J Med Case Rep 2017;11:119.
113. Russell N, Jennings S, Jennings B, Slee V, Sterling L, Castells M, et al. The mastocytosis society survey on mast cell disorders: part 2—patient clinical experiences and beyond. J Allergy Clin Immunol Pract 2019;7:1157-1165.e6.
114. Jennings S, Russell N, Jennings B, Slee V, Sterling L, Castells M, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. J Allergy Clin Immunol Pract 2014;2:70-6.
115. Shibao C, Arzubiaga C, Roberts LJ II, Raj S, Black B, Harris P, et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. Hypertension 2005;45:385-90.
116. Bonamichi-Santos R, Yoshimi-Kanamori K, Giavina-Bianchi P, Aun MV. Association of postural tachycardia syndrome and Ehlers-Danlos syndrome with mast cell activation disorders. Immunol Allergy Clin North Am 2018;38:497-504.
117. Doherty TA, White AA. Postural orthostatic tachycardia syndrome and the potential role of mast cell activation. Auton Neurosci 2018;215:83-8.
118. Colombi M, Dordoni C, Cinquina V, Venturini M, Ritelli M. A classical Ehlers-Danlos syndrome family with incomplete presentation diagnosed by molecular testing. Eur J Med Genet 2018;61:17-20.
119. Roma M, Marden CL, De Wandele I, Francomano CA, Rowe PC. Postural tachycardia syndrome and other forms of orthostatic intolerance in Ehlers-Danlos syndrome. Auton Neurosci 2018;215:89-96.
120. Qureshi AA, Friedman AJ. A review of the dermatologic symptoms of idiopathic mast cell activation syndrome. J Drugs Dermatol 2019;18:162-8.
121. Kohn A, Chang C. The relationship between hypermobile Ehlers-Danlos syndrome (hEDS), postural orthostatic tachycardia syndrome (POTS), and mast cell activation syndrome (MCAS). Clin Rev Allergy Immunol 2019:1-25.
122. Lyons JJ, Sun G, Stone KD, Nelson C, Wisch L, O'Brien M, et al. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. J Allergy Clin Immunol 2014;133:1471-4.
123. Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat Genet 2016;48:1564-9.

124. Lyons JJ. Hereditary alpha tryptasemia: genotyping and associated clinical features. Immunol Allergy Clin North Am 2018;38:483-95.
125. Schwartz LB, Sakai K, Bradford TR, Ren S, Zweiman B, Worobec AS, et al. The alpha form of human tryptase is the predominant type present in blood at baseline in normal subjects and is elevated in those with systemic mastocytosis. J Clin Invest 1995;96:2702-10.
126. Kanthawatana S, Carias K, Arnaout R, Hu J, Irani AM, Schwartz LB. The potential clinical utility of serum alpha-protryptase levels. J Allergy Clin Immunol 1999;103:1092-9.
127. Akin C, Soto D, Brittain E, Chhabra A, Schwartz LB, Caughey GH, et al. Tryptase haplotype in mastocytosis: relationship to disease variant and diagnostic utility of total tryptase levels. Clin Immunol 2007;123:268-71.
128. Sabato V, Van De Vijver E, Hagendorens M, Vrelust I, Reyniers E, Fransen E, et al. Familial hypertryptasemia with associated mast cell activation syndrome. J Allergy Clin Immunol 2014;134:1448-1450.e3.
129. Lyons JJ, Stotz SC, Chovanec J, Liu Y, Lewis KL, Nelson C, et al. A common haplotype containing functional CACNA1H variants is frequently coinherited with increased TPSAB1 copy number. Genet Med 2018;20:503-12.