

Mast cell activation syndromes



Cem Akin, MD, PhD Ann Arbor, Mich

Mast cell activation is common and possibly necessary for maintenance of survival. Disordered mast cell activation occurs when mast cells are pathologically overproduced or if their activation is out of proportion to the perceived threat to homeostasis. Mast cell activation syndrome refers to a group of disorders with diverse causes presenting with episodic multisystem symptoms as the result of mast cell mediator release. Despite introduction of diagnostic criteria and some advances in treatment in the last decade, many areas of mast cell activation syndrome are in need of research. This article reviews our current knowledge about the various types of mast cell activation disorders, their treatment, and areas of uncertainty in need of future investigation. (J Allergy Clin Immunol 2017;140:349-55.)

Key words: Mast cell, mastocytosis, mast cell activation syndrome, anaphylaxis, tryptase

Disorders manifested by mast cell activation encompass a broad variety of diseases that can range from very rare to very common. Mast cell activation can be caused by both IgE-mediated and non-IgE-mediated triggers. On the common end of the spectrum, atopic disorders, such as allergic rhinitis and allergic asthma, can affect up to 10% to 30% of the general population.¹ In contrast, mastocytosis and monoclonal mast cell activation syndrome (MMAS) might be as rare as 1 in 10,000 to 20,000 subjects.² Disorders caused by mast cell activation might not necessarily have the mast cell as the central pathogenic component. Rather, mast cells might be reacting to stimuli generated by another pathologic process. By their nature, mast cells are designed to detect and respond to triggers of internal or external stress or danger.³ Therefore some level of mast cell activation might be physiologic or even necessary to maintain normal homeostasis on a day-to-day basis. The question then is when mast cell activation becomes a disorder.

There are 2 circumstances in which mast cell activation would result in pathologic clinical symptomatology. The first is when mast cells are produced abnormally, either qualitatively or

Abbreviation used

MMAS: Monoclonal mast cell activation syndrome

quantitatively. This is the case in patients with clonal mast cell disorders in which the mast cell progenitor is affected by a neoplastic gain-of-function mutation, most commonly in *KIT*, a transmembrane receptor tyrosine kinase highly expressed by mast cells.⁴ The resulting neoplastic mast cells then accumulate in tissues and can interfere with tissue function or might release their mediators inappropriately, causing a variety of localized and systemic symptoms.

The second circumstance is when mast cell activation is out of proportion with the need to defend the body from the perceived danger. This might be the case when there is an imminent threat from infections, physical triggers, venoms, or allergens. An extreme example of inappropriate mast cell activation is anaphylaxis.

Mast cell activation can be localized or systemic. Examples of tissue-specific consequences of mast cell activation include urticaria, allergic rhinitis, and wheezing. Systemic mast cell activation presents with symptoms involving 2 or more organ systems (skin: urticaria, angioedema, and flushing; gastrointestinal: nausea, vomiting, diarrhea, and abdominal cramping; cardiovascular: hypotensive syncope or near syncope and tachycardia; respiratory: wheezing; naso-ocular: conjunctival injection, pruritus, and nasal stuffiness).⁵ This can result from release of mediators from a specific site, such as the skin or mucosal tissue, or activation of mast cells around the vasculature.

Mast cell activation syndrome designates a severe constellation of symptoms within the broader group of disorders of mast cell activation.⁶ Criteria for mast cell activation have been proposed and are shown in Table I.^{5,6} Because no single symptom is specific for mast cell activation, it is important to satisfy all 3 criteria before concluding that a given patient's symptoms are due to mast cell activation. Idiopathic anaphylaxis is a specific entity within the mast cell activation syndromes in which the patient meets the clinical diagnostic criteria of anaphylaxis.⁷ It should be noted that not all clinical presentations of systemic mast cell activation satisfy the criteria for anaphylaxis. For example, a patient can experience urticaria and gastrointestinal symptoms after exposure to a known or possible allergen. This presentation would be more appropriately termed mast cell activation syndrome than idiopathic anaphylaxis, as opposed to a patient who experiences hypotensive syncope or respiratory compromise (Fig 1 and Table II).

VALIDATED MARKERS OF MAST CELL ACTIVATION

Clinically available and validated markers of mast cell activation are shown in Table III. The most specific marker of

From the Division of Allergy and Clinical Immunology, University of Michigan.

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Corresponding author: Cem Akin, MD, PhD, University of Michigan, Division of Allergy and Clinical Immunology, 24 Frank Lloyd Wright Dr, PO Box 442, Suite H-2100, Ann Arbor, MI 48106-0442. E-mail: cemakin@med.umich.edu.

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TABLE I. Proposed criteria for mast cell activation syndrome (all 3 must be present)

1. Episodic multisystem symptoms consistent with mast cell activation
2. Appropriate response to medications targeting mast cell activation
3. Documented increase in validated markers of mast cell activation systemically (ie, either in serum or urine) during a symptomatic period compared with the patient's baseline values*

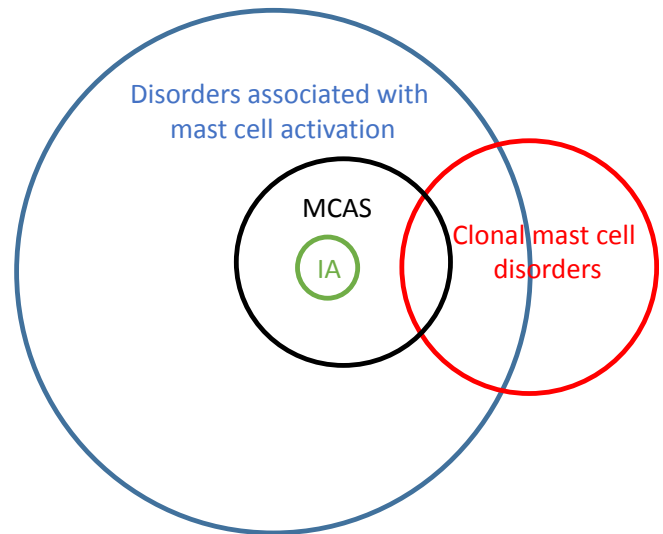
*Documentation of a single meaningful increase (see text) in tryptase level is sufficient, whereas it is recommended to document at least 2 measurements of increased levels of other markers.

mast cell burden and activation is tryptase.⁸ The normal median tryptase level is approximately 5 ng/mL. A serum or plasma level of greater than 11.4 ng/mL is considered increased. Although basophils and early myeloid cells produce trace amounts of tryptase, the great majority of the serum or plasma tryptase is derived from mast cells. Tryptases detectable in serum at baseline conditions are proenzymes that lack enzymatic activity and are excreted out of the cell (α -protryptase or β -protryptase). β -Protryptase is further enzymatically cleaved and processed to a mature tryptase with proteolytic activity.⁹ Mature tryptase is stored in mast cell granules and released during mast cell degranulation. It reaches its peak in circulation within 1 hour.

Release of mature tryptase into the circulation after a mast cell activation episode results in a transient increase in total measurable tryptase levels in serum. The formula of 20% baseline tryptase plus 2 ng/mL is suggested as a meaningful increase indicative of mast cell activation.⁶ Thus if the baseline tryptase level is 5 ng/mL in a given patient, a level of 8 ng/mL or greater within 4 hours of a suspected anaphylactic event confirms that mast cell activation has occurred in that patient. Serum tryptase levels should be measured within 4 hours after a suspected mast cell activation event because they return to baseline and might not be found to be increased after this time.

A study screening 15,298 patients in an allergy clinic found 5.9% of patients had increased tryptase levels. Patients with increased tryptase levels (>11.4 ng/mL) were more likely to experience severe anaphylactic reactions to venoms, drugs, and radiologic contrast media and had more complaints of fatigue, bloating, muscle/bone aches, vertigo, tachycardia, flushing, palpitations, diarrhea, and edema compared with patients with normal tryptase levels.¹⁰ Baseline tryptase levels can be found to be increased in patients with a number of conditions, including mastocytosis, mast cell hyperplasia, chronic kidney disease, myeloid neoplasms, spurious increase caused by assay interference, and familial hypertryptasemia.

Familial hypertryptasemia is a recently described phenotype with autosomal dominant inheritance resulting from duplication or triplication of the α -tryptase gene (*TPSAB1*) and is found in approximately 6% of the general population,¹¹ in which α -tryptase is overproduced in proportion to the gene dosage. These patients can present variably with a phenotype that can include retention of primary teeth, flushing, joint hypermobility, venom reactions, and functional gastrointestinal disorders, such as irritable bowel syndrome. However, it is not clear whether enzymatically inactive α -tryptase plays a direct role in the pathogenesis of these findings. Mast cells from patients with familial hypertryptasemia were not shown to be inherently hyperactive compared with subjects with normal tryptase levels. Therefore there are currently no data to suggest that patients with a

**FIG 1.** Relationship between clonal mast cell disorders, mast cell activation syndrome (MCAS), and idiopathic anaphylaxis (IA). Circle sizes do not represent prevalence.

tryptase level increased caused by familial hypertryptasemia have an activated mast cell phenotype.

Urinary metabolites of histamine have been validated to correlate with mast cell burden and activation.¹² The most commonly measured metabolites are N-methyl histamine (a product of histamine N-methyltransferase) and 1-methyl-4-imidazole acetic acid (a product of diamino-oxidase). Twenty-four-hour samples are recommended, although shorter collection times or spot analyses are also acceptable. Measuring blood histamine levels as a marker of mast cell activation is not recommended because they are often derived from basophils at baseline and can be influenced by a variety of factors, including obtaining and storing the blood sample. Likewise, urinary histamine levels can be influenced by bacterial flora of the urinary tract, storage conditions, and diet.

Prostaglandin D₂ is a known marker of mast cell activation.¹³ Its metabolite 11- β -prostaglandin F₂ α can be measured in urine as a marker of mast cell activation.¹⁴ However, this mediator is not specific for mast cell activation. A number of immune cells, including eosinophils, and nonimmune cells are capable of producing prostaglandin D₂ through 2 structurally different enzymatic pathways. Therefore it is not recommended to rely solely on a single measurement of an increased prostaglandin D₂ or F₂ α level as a marker of mast cell activation unless one of the other markers are also present in the patient. Furthermore, cutoffs for significantly increased levels for mediators other than tryptase are not established for mast cell activation. In patients with *bona fide* mast cell activation with increased prostaglandin levels, aspirin therapy has been used with some success.¹⁴

Leukotriene C₄ is a lipid mediator released during mast cell activation.¹³ It is metabolized into leukotriene D₄, which is then converted to leukotriene E₄ and can be detected in the urine.¹⁵ Although there has not been extensive experience to correlate leukotriene E₄ levels in urine with various mast cell symptoms, its measurement might help guide treatment of the symptoms with leukotriene-modifying drugs. Other markers for mast cell activation include heparin and fibrinogen cleavage products. Plasma heparin activity was reported to be increased in patients

TABLE II. Comparison of idiopathic anaphylaxis and mast cell activation syndrome

Feature	Idiopathic anaphylaxis	Mast cell activation syndrome
Symptoms occur in well-defined episodes	Yes	Yes
Increased markers of mast cell activation during episodes	Yes (but absence of laboratory confirmation does not exclude the diagnosis if the patient meets the clinical definition of anaphylaxis)	Yes (required for diagnosis)
Positive response to mast cell–targeting medications	Yes	Yes
Presence of respiratory compromise or hypotension during episodes	+	+/–
Might be associated with clonal (mastocytosis or MMAS), IgE-mediated, or non-IgE-mediated trigger of mast cell activation	–	+

TABLE III. Clinically available and validated markers of mast cell activation

Marker	Comment
Tryptase	The most specific marker Almost always increased in patients with hypotensive mast cell activation episodes Must be measured within 4 h of an episode and compared with baseline values Increased baseline levels in the absence of renal disease or myeloid neoplasm might indicate mastocytosis or familial hypertryptasemia
Urinary histamine metabolites	Fairly specific for mast cell activation Might be influenced by diet or bacterial contamination Specific cutoffs for mast cell activation syndrome not established
Urinary prostaglandin D ₂ or metabolites	Increased in patients with mast cell activation Not specific to mast cells Specific cutoffs for mast cell activation not established Not recommended as the single marker of mast cell activation Can guide the decision to initiate aspirin therapy if the patient is not allergic to nonsteroidal anti-inflammatory drugs
Urinary leukotriene E ₄	Increased in patients with mast cell activation Less clinical experience than other markers Might guide the decision to initiate leukotriene-targeting therapy

with mast cell activation symptoms,¹⁶ and the α -chain of fibrinogen is cleaved by β -tryptase.¹⁷ These assays, however, are not routinely used in general practice, and clinically significant bleeding is rare in patients with anaphylaxis.

CLINICAL VARIETY OF MAST CELL ACTIVATION SYNDROMES

Mast cell activation syndromes can be divided into primary, secondary, and idiopathic.^{5,6} Primary disorders of mast cell activation result from a defect in the mast cell progenitor, leading to abnormal qualitative or quantitative production of mast cells. These include 2 major subgroups: mastocytosis and MMAS.

Mastocytosis is a disorder characterized by abnormal proliferation and accumulation of mast cells deriving from a clonal progenitor carrying a gain-of-function mutation in *KIT*.^{4,18} The

most common *KIT* mutation is D816V, which involves the intracellular tyrosine kinase portion of the gene.¹⁹ *KIT* is involved in differentiation, proliferation, and protection from apoptosis in mast cells. Although *in vitro* data suggest that pathways involved in *KIT* signal transduction cooperate with IgE-mediated pathways of mast cell activation,²⁰ involvement of the gain-of-function *KIT* mutations in these activation pathways remain to be proved.

Pathologic mast cell infiltrates in mastocytosis are most commonly detected in bone marrow and skin. Consequently, diagnosis is established by inspecting the skin and performing a skin or bone marrow biopsy. The current World Health Organization classification of mastocytosis includes 7 categories (Table IV).^{4,6,18} Mast cell activation symptoms can be seen in any of these categories.

Cutaneous mastocytosis is most commonly present in children and by definition presents with lack of involvement of internal organs, such as bone marrow. Because more than 90% of childhood-onset mastocytosis resolves by adolescence, invasive investigations, such as bone marrow biopsies, are not recommended unless the child has an abnormal complete blood count with differential, hepatosplenomegaly, or persistently increased tryptase levels of greater than 20 ng/mL, which do not decrease with time.²¹ Patients with cutaneous mastocytosis can experience mast cell activation events. These events might be limited to the skin in the form of flushing and urticaria but can also involve non-cutaneous sites, such as gastrointestinal or cardiovascular systems. The presence of noncutaneous symptoms does not necessarily indicate systemic disease because mast cells activated in the skin are capable of releasing mediators that act distally. Children with cutaneous mastocytosis can carry atypical *KIT* mutations that involve the extracellular parts of the gene instead of codon 816, as seen in typical adult-onset systemic mastocytosis.²² It is not clear whether the clinical phenotype is dictated by the mutation present in these patients.

Approximately 10% of childhood-onset cutaneous mastocytosis can persist into systemic mastocytosis and present with bone marrow infiltrates. A rare histopathologic variant called well-differentiated systemic mastocytosis can be seen in these children with systemic disease.^{23,24} Patients with well-differentiated systemic mastocytosis lack the pathologic expression of CD25, have mast cells with normal morphology, and might lack the *KIT* D816V mutation. Patients with systemic mastocytosis present with bone marrow involvement that satisfy the pathologic diagnostic criteria of the World Health Organization (Table V). The major and 1 minor or 3 minor criteria are required to establish a diagnosis of systemic mastocytosis. Occasionally, it is possible

TABLE IV. World Health Organization classification of mastocytosis*

Cutaneous mastocytosis
Indolent systemic mastocytosis
Smoldering systemic mastocytosis
Mastocytosis with an associated hematologic neoplasm
Aggressive systemic mastocytosis
Mast cell leukemia
Mast cell sarcoma

*See Valent et al^{4,18} for a detailed discussion of mastocytosis variants.

to make a diagnosis of systemic mastocytosis from a biopsy specimen that does not involve bone marrow. The same criteria apply to the non-bone marrow biopsies. Gastrointestinal biopsies present a particular challenge because mast cells in the gastrointestinal tract can be negative for tryptase expression, and therefore CD117 staining should be performed.²⁵ In addition, mast cells in the gastrointestinal tract can be increased in patients with a number of other conditions, including irritable bowel syndrome, which can lead to the incorrect diagnosis of gastrointestinal mastocytosis if the other pathologic criteria are absent in these biopsy specimens.

MMAS is a term coined to designate patients who present with symptoms of mast cell activation (often diagnosed as idiopathic anaphylaxis) and lack cutaneous findings and have either the *KIT* D816V mutation or CD25⁺ mast cells in their bone marrow.^{6,26} These patients have tryptase levels of less than 20 ng/mL and have a normal to low burden of mast cells and therefore do not satisfy the full criteria for the diagnosis of systemic mastocytosis. Although some of these patients can be found to have systemic mastocytosis on future biopsies, personal experience suggests that most patients do not progress to meet the full criteria for systemic mastocytosis. Spontaneous resolution of MMAS or systemic mastocytosis has not been described to date.

Diagnosis of MMAS requires a high degree of clinical suspicion and confirmation by means of bone marrow biopsy. The diagnosis should be considered in patients presenting with symptoms of hypotensive anaphylaxis. *KIT* D816V mutational analysis with an allele-specific PCR method can be used as a screening tool in these patients. Patients positive for this mutation should be referred for bone marrow biopsy, although the absence of this mutation in peripheral blood does not rule out MMAS.

The presentation of mast cell activation syndrome in patients with primary mast cell disorders involves cutaneous flushing, tachycardia, hypotension, and gastrointestinal cramping, nausea, vomiting, and diarrhea (Box 1). Chronic urticaria is almost never associated with systemic mastocytosis.²⁷ Likewise, angioedema and upper airway symptoms are highly atypical in patients with mastocytosis but can be seen in cases of secondary or idiopathic mast cell activation. Patients with mastocytosis or monoclonal mast cell activation are more prone to Hymenoptera venom hypersensitivity.²⁸ These patients have evidence of IgE-mediated sensitization determined based on either skin or blood testing and an increased burden of mast cells, making them particularly susceptible for life-threatening events after Hymenoptera stings. Therefore a serum tryptase level at baseline should be incorporated into the routine workup of patients with systemic reactions to Hymenoptera stings. Currently, it is recommended that patients with systemic venom hypersensitivity who have an associated

TABLE V. Diagnostic criteria for systemic mastocytosis

Major and at least 1 minor criterion or 3 minor criteria are required for diagnosis
Major: Multifocal aggregates of ≥ 15 mast cells in a noncutaneous tissue biopsy specimen
Minor
Aberrant mast cell morphology (eg, spindle-shaped, hypogranulated, aberrant nucleus)
Aberrant CD25 and/or CD2 expression on mast cells*
Presence of a codon 816 <i>KIT</i> mutation in blood or lesional tissue*
Serum baseline tryptase level >20 ng/mL (not valid if the patient has another hematologic neoplasm)

*Markers of mast cell clonality.

primary mast cell disorder be initiated on venom immunotherapy and maintained indefinitely on this treatment.

In patients with secondary mast cell activation syndrome, mast cells are produced normally in the bone marrow and are generally present in normal numbers in tissues or can be increased (reactive mast cell hyperplasia) in response to the inflammatory milieu. The inciting trigger for mast cell activation can be IgE mediated (food, drug, Hymenoptera venom, or inhalant) and can be identifiable by an allergy workup. Non-IgE-mediated mast cell activation triggers include drugs; physical stimuli, including exercise; stress; acute or chronic infections; venoms; or another inflammatory or neoplastic disease. Through the polycationic secretagogue receptor MRGPRX2, mast cells are capable of detecting and responding to a variety of triggers, including substance P, drugs, and venom components.²⁹ Mast cells also have pattern recognition receptors, complement receptors, and IgG receptors that can act as sensors of surrounding inflammation.^{30,31}

In some patients, despite extensive workup, no clear cause for the mast cell activation episodes is found.⁵ These patients are termed to have idiopathic mast cell activation syndrome. Idiopathic anaphylaxis is a subgroup of this category. However, for historic reasons, the author prefers to use the term idiopathic anaphylaxis in patients who meet the clinical criteria for anaphylaxis. These patients might have a clonal or secondary cause identified and can be reclassified as more data become available.

MANAGEMENT OF MAST CELL ACTIVATION SYNDROMES

General principles of the management of mast cell activation syndromes include avoidance of triggers, pharmacologic management of the actions of mast cell mediators, treatment of the associated conditions, and consideration of mast cell cyoreduction in those with primary (clonal) mast cell disorders.³²

Avoidance of triggers

An allergy workup can be used as guidance to avoid food, medication, and inhalational triggers of mast cell activation. Patients with systemic venom reactions should be maintained on venom immunotherapy indefinitely. Immunotherapy to inhalant allergens can be considered on a case-by-case basis depending on the risk/benefit ratio for each patient. Although general statements of avoidance of specific triggers are not appropriate for all patients, emotional stress is a major trigger factor for all groups of

Box 1. Mast cell activation syndrome: Clinical pearls

Chronic urticaria, angioedema, and upper airway swelling are almost never associated with mastocytosis, and a bone marrow biopsy is not necessary in these patients.

Chronic urticaria and angioedema can be a feature of secondary (IgE- and non-IgE-mediated) and idiopathic mast cell activation syndromes. Therefore appropriate workup should focus on identifying or ruling out such possible causes.

A baseline serum tryptase level should be measured in all patients with hypotensive anaphylaxis and those with systemic reactions to Hymenoptera.

The presence of hypotension during anaphylaxis increases the odds of clonal mast cell disease. Therefore there should be a low threshold to refer these patients for a bone marrow biopsy, regardless of tryptase levels, if an IgE-mediated cause does not explain all episodes.

mast cell activation syndromes and therefore should be managed appropriately by using pharmacologic or nonpharmacologic methods. Possible mechanisms of stress-induced mast cell activation can include corticotropin-releasing factor and substance P.³ There are no controlled clinical studies to show that low-histamine diets are helpful in management of mast cell activation symptoms, although individual patients can respond differently.

Pharmacologic management

The mainstays of treatment of mast cell activation symptoms are H₁- and H₂-histamine receptor antagonists, leukotriene-modifying agents, cromolyn sodium, glucocorticoids, and omalizumab. Urinary markers of mast cell mediators can be used as guidance when selecting appropriate antimediation therapy. Self-injectable epinephrine should be prescribed to all patients with a history of anaphylactic episodes and should be considered for those with mastocytosis, even if they do not have a history of anaphylaxis. Ketotifen is an antihistamine that has been shown to be helpful in patients with idiopathic anaphylaxis.³³ This medication is not available in oral form in the United States. Cromolyn sodium has been used in patients with mastocytosis with gastrointestinal symptoms, but it has a very poor absorption, limiting its efficacy as a systemic medication.³⁴ The starting regimen would include once or twice daily nonsedating H₁-receptor antagonists, which can be combined with an H₂-receptor antagonist if gastrointestinal symptoms are present. This regimen can be supplemented with as-needed use of a shorter- or longer-acting antihistamine. Patients with severe refractory symptoms can benefit from the addition of a glucocorticoid. The lowest dose of glucocorticoid should be found, which maintains the appropriate control of symptoms. Leukotriene antagonists, such as montelukast or zileuton, can also be used as second-line and add-on therapies; however, the side effects of these medications, including psychiatric side effects, should be discussed with the patient before their use. Omalizumab has been shown to benefit patients with primary and secondary and idiopathic mast cell activation and has been used as an adjunctive treatment to allow tolerance of venom immunotherapy.³⁵⁻³⁷ The mechanism of action of omalizumab in patients with non-IgE-mediated mast cell activation syndromes is unclear but might suggest the presence of an

TABLE VI. Mast cell activation syndrome: What is unknown?

1. Is there a chronic form of mast cell activation syndrome in which patients present with multiple symptoms that can be caused by but not specific to mast cell mediators? Is the total body mast cell burden capable of maintaining a continuous state of mast cell activation in such patients?
2. Is there a yet-to-be identified clonal or secondary (eg, IgE-mediated) cause in patients with idiopathic mast cell activation syndrome? How does omalizumab work in patients with non-IgE-mediated mast cell activation syndrome?
3. What are additional clinically useful markers of mast cell activation?
4. Is there pathologic mast cell activation in patients with joint hypermobility and postural orthostatic tachycardia syndrome?
5. Is there a confirmed clinical phenotype in patients with familial hypertryptasemia? If so, are tryptase or mast cells involved in its pathogenesis?

unidentified endogenous IgE target or hyposensitization of mast cells through downregulation of nonspecific IgE receptors.

Mast cell cyto reduction

The traditionally used mast cell cyto reductive agents IFN- α and cladribine have also been shown to control mast cell activation episodes in patients with mastocytosis.³⁸⁻⁴¹ These agents are generally prescribed to patients with advanced variants of mastocytosis, such as those presenting with associated hematologic disorders and aggressive systemic mastocytosis or mast cell leukemia. They can be considered on rare occasions in patients with indolent mastocytosis with life-threatening mast cell activation episodes that do not respond to anti-mediator therapies.

Midostaurin, a multikinase inhibitor with activity against D816V *KIT*, has been approved recently by the US Food and Drug Administration for treatment of advanced mastocytosis. Patients receiving midostaurin in addition to mast cell cyto reduction also experienced reduction in mast cell activation symptoms and have had increases in their quality of life.⁴² Midostaurin has also been shown to decrease IgE-mediated mast cell activation.⁴³ The common side effects of the drug include nausea and vomiting, and monitoring of complete blood count is required for cytopenias. This medication is currently not approved for patients with indolent mastocytosis or nonclonal mast cell disorders.

Other signal transduction inhibitors

In a recent clinical trial, the prototypic tyrosine kinase inhibitor imatinib, which has activity against wild-type *KIT* and platelet-derived growth factor receptor, has been shown to result in increased FEV₁ and decreased airway hyperresponsiveness in patients with severe asthma.⁴⁴ It also resulted in a decrease in mast cell tryptase levels and mast cell numbers in lung biopsy specimens. However, the conclusive evidence causally linking the improvement in lung function to a decrease in mast cell activation is lacking. *In vitro* imatinib does not decrease mast cell activation, and therefore it is not recommended for treatment of nonclonal mast cell activation syndromes or those with mastocytosis carrying the D816V *KIT* mutation, which confers resistance to this drug.

Masitinib, an inhibitor of wild-type (but not D816V mutated) *KIT* and *LYN*, has been reported to improve symptoms in a phase

III trial in patients with indolent systemic or smoldering mastocytosis (cumulative response rate of 18.7% vs 7.4% placebo).⁴⁵ Diarrhea, rash, and asthenia were reported as frequent side effects in 11%, 6%, and 6% of patients, respectively.

Ibrutinib is a Bruton tyrosine kinase inhibitor approved by the US Food and Drug Administration for treatment of mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenstrom macroglobulinemia. A recent study showed decreased allergy skin test and basophil activation test responses in 2 patients prescribed ibrutinib for lymphoproliferative disease.⁴⁶ The drug had no effect on nonspecific non-IgE-mediated mast cell activation. This is consistent with described *in vivo* effects of Bruton tyrosine kinase inhibitors on IgE-mediated mast cell activation⁴⁷; however, more data are required, especially in regard to its adverse effects on antibody-mediated immune function, before it can be considered in treatment of IgE-mediated disease.

AREAS OF UNCERTAINTY AND OPPORTUNITIES FOR RESEARCH

In clinical practice some patients with a variety of multisystem symptoms who do not have an identifiable central cause for their complaints are referred for investigation of mast cell activation syndrome. These symptoms can include chronic fatigue; intolerances to various environmental factors, foods, and medications; and neuropsychiatric findings, including memory problems and headaches. These complaints can be present on a chronic basis without well-defined attacks or episodes of mast cell activation. Currently, there is no evidence to suggest that an abnormal mast cell phenotype that results in ongoing chronic mediator release is responsible for these symptoms. Some of these patients can have a slightly increased basal tryptase level that might have led to the diagnosis of mast cell activation. Familial hypertryptasemia should be strongly considered in these patients because its prevalence in the general population appears to be as high as 6%. There are also clinical observations of patients who present with hypermobility-type Ehlers-Danlos syndrome and postural orthostatic hypotension who also have various symptoms of mast cell activation, such as flushing and gastrointestinal complaints.^{48,49} A subset of patients with hyperadrenergic postural orthostatic tachycardia syndrome were reported to present with increased urinary histamine metabolites and are more likely to experience flushing, shortness of breath, headaches, diuresis, and gastrointestinal symptoms.⁵⁰ More research is clearly needed in these areas because it is not clear whether symptoms attributable to mast cell activation in these patients result from mast cell mediator release or are caused by another pathologic process, such as dysautonomia, defective connective tissue, or both (Table VI).

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