Mast Cell Activation Disorders

Cem Akin, MD, PhD *Boston, Mass*

Disorders associated with mast cell activation range from relatively common IgE-mediated disease and chronic urticaria to rarer conditions such as mastocytosis or monoclonal mast cell activation disorder. Mast cell activation disorders can be mechanistically classified into primary (associated with abnormal production of mast cells that carry pathologic markers of clonality), secondary (normal mast cells activated in reaction to a microenvironmental trigger), and idiopathic (no etiology is found). Clinical presentations, diagnostic criteria as well as general principles of a stepwise therapy approach are discussed. **(J Allergy Clin Immunol Pract 2014;2:252-7)**

Key words: *Mast cells; Mastocytosis; Mast cell activation syndromes; Diagnosis; Treatment; Tryptase c-kit*

INFORMATION FOR CATEGORY 1 CME CREDIT: Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please first read the instructions for this article on page 257.e1.

Mast cells are evolutionarily conserved cells of the immune system capable of responding to allergen specific as well as nonspecific danger signals.[1,2] Allergen-specific responses are mainly conferred by surface-bound specific IgE molecules synthesized in individuals atopically sensitized. Nonspecific triggers of mast cell activation include physical factors (such as changes in internal or external temperature, pH, pressure, and pain), microbial components (via Toll-like receptors), complement activation products, emotional stress, and drugs. Some triggers, for example, Hymenoptera venoms, are capable of activating mast cells via both IgE and non-IgE mediated mechanisms. Mast cells are located in tissues at interfaces with external environment, such as skin and mucosa, gastrointestinal tract, respiratory system, and ocular conjunctiva, in close proximity to blood vessels and nerves as well as interstitially distributed in bone marrow, liver, spleen, and lymph nodes. Their wide tissue distribution and ability to be activated by a variety of signals makes it a rather universal occurrence for humans to experience symptoms caused by mast cell activation either sporadically or chronically. These symptoms may range from tissue-specific events such as localized itching or nasal congestion to more system-wide symptoms that result from wide-spread mast cell activation and may lead to the potentially life-threatening outcome of anaphylaxis.

Mast cell activation results in the release of mediators from 3 major compartments.[3] Within minutes of activation, mast cell degranulation leads to release of preformed mediators stored in mast cell granules, including histamine and proteases (mainly tryptase). Mast cell degranulation is followed by *de novo* synthesis of membrane lipid–derived mediators, particularly prostaglandin (PG) D2 and cysteinyl leukotrienes (LTC4, D4, and E4). Also, mast cell activation results in synthesis of a variety of pro- and anti-inflammatory cytokines and chemokines, including TNF, IL-1, IL-4, IL-5, IL-8, IL-13, IL-1RA, and chemokine (C-C motif) ligand 2. Mast cell inflammatory mediator profile (especially protease content) shows heterogeneity according to the tissue microenvironment, and release of mast cell products and symptoms, therefore, may differ according to the tissue in which mast cell activation occurs and possibly the trigger that causes the mast cell activation. The location of the activated mast cells and the mediators released determine the clinical symptoms.

LOCALIZED VERSUS SYSTEMIC MAST CELL ACTIVATION

Allergist/immunologists are the primary specialists who care for symptoms of mast cell activation. Upon encountering a patient with mast cell activation symptoms, the physician should first assess whether the symptoms are localized or systemic. Localized-tissue–specific mast cell activation generally occurs in the context of well-recognized clinical entities, such as contact urticaria, allergic rhinitis, or asthma, and the symptoms, in most instances, are limited to the area of the interaction with the trigger, although generalized-tissue–specific symptoms also are possible such as in the case of chronic idiopathic urticaria. Systemic mast cell activation reactions involve or have clinical consequences in more than 1 organ system. The best recognized systemic mast cell activation disorder is systemic anaphylaxis.[4] Some patients with systemic mast cell activation may have lesser severity of symptoms that do not meet the definition of anaphylaxis (eg, a patient with recurrent generalized urticaria associated with exquisite abdominal pain), and these patients are appropriate to be considered for a diagnosis of mast cell activation syndrome (MCAS).[5]

MECHANISTIC CLASSIFICATION OF MAST CELL ACTIVATION DISORDERS

Once the mast cell activation symptoms are recognized, further workup is necessary to place the disorder into one of the mechanistic categories (Table I).[5] As part of this workup, the physician

Mastocytosis Center, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass

No funding was received for this work.

Conflicts of interest: C. Akin has received consultancy fees from Novartis and Patara Pharma; has received research support from Dyax; and has a patent for an LAD2 cell line with the National Institutes of Health.

Received for publication March 11, 2014; revised manuscript received and accepted for publication March 24, 2014.

Corresponding author: Cem Akin, MD, PhD, Mastocytosis Center, Brigham and Women's Hospital, 1 Jimmy Fund Way, Room 626B, Boston, MA 02115. E-mail: cakin@partners.org.

2213-2198/$36.00

http://dx.doi.org/10.1016/j.jaip.2014.03.007

Abbreviations used
AHNMD- Associated hematologic clonal non–mast cell disease
MCAS- Mast cell activation syndrome
MMAS- Monoclonal mast cell activation syndrome
PG- Prostaglandin
VIT- Venom immunotherapy
WHO- World Health Organization

often considers whether the symptoms could be attributed to an IgE-mediated allergy (environmental, food, drug, or Hymenoptera). If the patient history and/or diagnostic workup are not consistent with an IgE-mediated trigger, then non-IgE mediated causes of nonspecific mast cell activation should be considered. These may include chronic infections, autoimmune disorders, neoplasias, and physical urticaria and/or anaphylaxis syndromes. For example, patients with SLE,[6] antiphospholipid syndrome,[7] and thyroid autoimmunity[8] may present with chronic idiopathic (spontaneous) urticaria and angioedema. The link between infections and urticaria and dermographism has been well recognized.[9] Viral upper respiratory tract or gastrointestinal infections are the most common cause of acute urticaria in children. Gastrointestinal infections with bacterial, viral, and parasitic pathogens (including *Helicobacter pylori, Yersinia, Norovirus, Blastocystis, Giardia, Anisakis*), and dental and upper respiratory bacterial infections have been reported to be associated with chronic spontaneous urticaria (see review in Wedi et al[9]). Severe itching and new onset eczema is a common symptom in lymphomas.[10,11] Patients with eosinophilic esophagitis have abundant mast cells in inflamed mucosa, which may contribute to fibrosis and esophageal rings.[12] Finally, if no IgE-mediated or secondary (reactive) cause has been found, then the patient may be considered for the diagnoses of a primary mast cell activation disorder, idiopathic anaphylaxis, or idiopathic MCAS.

PRIMARY MAST CELL DISORDERS

Primary mast cell activation disorders (also referred to as clonal mast cell disorders) are characterized by abnormal production of mast cells in the bone marrow. There are 2 major entities classified as a primary mast cell disorder: (1) mastocytosis and (2) monoclonal MCAS (MMCAS).[5,13] Both of these diagnoses should be substantiated by objective pathologic findings as stated in the World Health Organization diagnostic criteria (Table I).[14,15] Mastocytosis is a disorder caused by an abnormal and pathologic increase in mast cells in tissues, such as skin, bone marrow, and in other internal organs, such as liver, spleen, and lymph nodes.[16] It has 7 distinct categories with different clinical features and prognosis (Table I). Mastocytosis is associated with activating somatic mutations in the c-kit gene in the majority of cases.[17,18] Approximately 80% of children with cutaneous mastocytosis and >90% adults with systemic mastocytosis carry c-kit mutations. The most common c-kit mutation is D816V in exon 17, which is found in almost all adult patients and in 40% of pediatric patients. These mutations affect either the immediate mast cell progenitor or the multipotential hematopoietic progenitor, which give rise to mast cells and other blood cells.[19] In the latter case, patients have a high incidence of coexisting hematologic disorders, such as myelodysplastic or myeloproliferative syndromes, and are more likely to show progression of disease into a more advanced category.[20]

Patients suspected to have mastocytosis should have a thorough skin examination to look for the finding of urticaria pigmentosa or other rarer forms of mastocytosis (solitary mastocytoma or telangiectasia macularis eruptive perstans).[21,22] Urticaria pigmentosa lesions are fixed hyperpigmented maculopapular lesions and tend to spare the sun-exposed "public" areas, such as the face and hands. The exception is pediatric onset cutaneous mastocytosis, which can occur on the face and scalp. Although the lesions are fairly characteristic, a skin biopsy specimen should be obtained to confirm the diagnosis if there is any doubt. Immunohistochemical staining with tryptase is the preferred method of visualizing mast cells in tissues, including skin. Metachromatic stains such as Giemsa or toluidine blue also can be used in skin but are not reliable in extracutaneous tissues. Patients with MMAS do not meet the criteria for mastocytosis but have 1 or both clonal markers, that is, c-kit D816V mutation or CD25 expression. Although some of these patients may be detected to have indolent systemic mastocytosis (ISM), with follow-up, progression into an advanced poor prognostic category of mastocytosis has not been described.[13,23]

WHEN TO CONSIDER BONE MARROW BIOPSY IN MAST CELL ACTIVATION AND SUSPECTED MASTOCYTOSIS

The diagnosis of mastocytosis is greatly helped by the presence of urticaria pigmentosa (UP) lesions; however, approximately 20% of patients with mastocytosis may not have skin lesions. The diagnosis in these patients is suspected on the basis of recurrent unexplained mast cell activation symptoms. Hypotension, syncopal, and presyncopal events are more common in mastocytosis, whereas urticaria and angioedema are rarely seen during mast cell activation symptoms in mastocytosis.[24] Diarrhea, abdominal cramps, nausea, vomiting, and flushing are equally seen in mastocytosis and nonclonal secondary or idiopathic mast cell activation disorders. A baseline tryptase level along with clinical symptoms is helpful to decide whether further diagnostic workup for mastocytosis should be pursued.[25] In our practice, we consider a bone marrow biopsy of patients with baseline tryptase levels higher than 20 ng/mL or those who have syncopal or presyncopal events as part of their symptomatology (regardless of tryptase levels), whereas the presence of chronic urticaria or angioedema would be a deterrent to recommend this procedure. Some European centers use a higher tryptase level cutoff (25-30 ng/mL) in patients without skin lesions because it is not unusual to encounter patients with tryptase level ranges up to 40 ng/mL without evidence of mastocytosis.[26,27] It should be noted that tryptase levels can be found to be in normal ranges in patients with MMAS and those with limited ISM, whereas elevated tryptase levels (generally not exceeding 40 ng/mL) can be found in other myeloid neoplasms, renal failure, bone marrow suppression states, and chronic urticaria.[28-32] During this decision process, analysis of peripheral blood for D816V c-kit mutation can also be considered. The presence of the mutation in peripheral blood would help in deciding whether the patient needs a bone marrow biopsy, whereas its absence does not rule out mastocytosis because the mutation can still be present in lesional mast cells in bone marrow or skin. The age of the patient also matters when deciding on a bone marrow biopsy. We recommend a bone marrow biopsy in all adult patients with urticaria pigmentosa because almost all patients in this group have evidence of bone marrow involvement. Most

TABLE I. Global classification and diagnostic guidelines for disorders of mast cell activation

Category	Comments
1. Primary: (a) mastocytosis: cutaneous mastocytosis, indolent SM, SM-AHNMD, aggressive SM, mast cell leukemia, mast cell sarcoma, extracutaneous mastocytomas; (b) MMCAS	Cutaneous mastocytosis is diagnosed by inspection of skin lesions and skin biopsy
	Systemic mastocytosis is diagnosed according to the WHO criteria. 1 major + 1 minor 3 minor criteria are needed:
	Major criterion: multifocal aggregates of mast cells with >15 cells per aggregate in bone marrow or another extracutaneous tissue
	Minor criteria: 1. morphologic abnormalities in >25% of mast cells (spindled shapes) in infiltrate; 2. aberrant CD2 or CD25 expression by mast cells, 3. detection of a codon 816 c-kit mutation (commonly D816V), 4. baseline tryptase >20 ng/mL
	MMCAS is diagnosed when there is 1 marker or both markers of clonality (CD25 expression and/or c-kit D816V mutation) without other criteria
2. Secondary (a) IgE mediated; (b) non-IgE mediated: (i) mast cell activation associated with chronic inflammatory or neoplastic disorders, (ii) physical urticarias, (iii) chronic autoimmune urticaria	These disorders comprise a wide variety of clinical presentations, and the diagnosis should be established according to the guideline of the specific disease entity
3. Idiopathic: (a) urticaria, (b) angioedema, (c) anaphylaxis, (d) MCAS	Idiopathic urticaria, angioedema, and anaphylaxis are clinical diagnoses but should be substantiated by objective documentation of physical findings and tryptase levels (for idiopathic anaphylaxis) when possible.
	The following diagnostic criteria are proposed for idiopathic systemic mast cell activation that does not meet the criteria for anaphylaxis:
	1. Symptoms that involve more than 1 organ system: (a) nasocular and respiratory: nasal congestion, wheezing, conjunctival erythema, itching, and watering; (b) skin and soft tissues: urticaria, angioedema, itching; (c) gastrointestinal: nausea, vomiting, abdominal cramping, diarrhea; (d) cardiovascular: flushing, tachycardia, hypotension
	2. Favorable response to mast cell mediator targeting agents
	3. Elevation of a validated marker of mast cell activation during a symptomatic period; the most reliable marker is serum tryptase (see text for details)

AHNMD, Associated hematologic clonal non−mast cell disease; *SM,* systemic mastocytosis; *WHO,* World Health Organization.

pediatric patients with onset of skin lesions in the first 2 years of life, however, have disease limited to the skin and watchful waiting is appropriate in these patients unless they have another indication to do a bone marrow biopsy (eg, unexplained abnormalities in a complete blood cell count with differential, liver, spleen, or lymph node enlargement, or progressively increasing tryptase levels higher than 20 ng/mL).[33] The reason to do the bone marrow biopsy is as follows:

1. To look for tissue diagnostic evidence of systemic mastocytosis to fulfill World Health Organization criteria. Although an occasional patient can meet these criteria in another tissue biopsy, such as gastrointestinal biopsy or lymph node, all of those patients also have bone marrow involvement.
2. To assess tissue burden of mast cells, which can serve as a comparison if the patient has progressive symptoms in the future.
3. To rule out non−mast cell hematopoietic involvement.

It is important not to rely on routine hematoxylin and eosin staining to rule out mastocytosis because small mast cell collections can easily be missed on routine diagnostic microscopic examination. The recommended immunohistochemical stains for mastocytosis in bone marrow biopsy specimens are tryptase, CD117, and CD25. Once the diagnosis of mastocytosis is established, the patient should be classified into 1 of the 7 World Health Organization categories (Table I). It is not the scope of this article to discuss clinical and diagnostic features of these categories in detail; however, the most common category that presents with mast cell activation symptoms is indolent systemic mastocytosis, although patients in any category can have these symptoms.

Causes of mast cell activation episodes in mastocytosis are usually non-IgE mediated (such as heat, exercise, stress, spicy foods), with the notable exception of Hymenoptera anaphylaxis. A large series of patients (n = 379), in an Italian cohort, who had systemic reactions to Hymenoptera stings were checked for baseline tryptase, and those with an elevated tryptase level, of >11.4 ng/mL, underwent bone marrow examinations.[34] The results showed that the majority of patients with elevated tryptase levels (approximately 12% of the whole cohort) had mastocytosis or MMAS. It appears that elevated tryptase levels confer a risk for serious Hymenoptera reactions regardless of the presence of

mastocytosis. Patients with mastocytosis are recommended to have venom immunotherapy (VIT) indefinitely because systemic reactions have been reported after stopping VIT.[35] These patients also may be more likely to experience allergic reactions during immunotherapy, and the protection afforded by VIT may not be as high as a patient with a normal tryptase level or without mastocytosis.[36,37]

Adverse reactions to drugs may involve both IgE and non-IgE mechanisms, and sometimes can be the presenting manifestation (eg, perioperative anaphylaxis) of mastocytosis.[38] Most commonly implicated drugs are opioids, nonselective noninflammatory drugs, and muscle relaxants; however, with appropriate precautions, such as premedications and thoughtful selection of drugs perioperatively, successful outcomes are achieved for the great majority of patients (refer to www.tmsforacure.org for a list of medications safer to use in mastocytosis). The presence of multiple drug intolerances or "multiple chemical and food sensitivities" is not strongly associated with mastocytosis.

Mastocytosis or MMAS can be the underlying diagnosis in a significant subset of patients who were previously diagnosed as "idiopathic anaphylaxis." The initial study that reported this association found markers of mast cell clonality in bone marrow examinations in 5 of 12 patients, all of whom had recurrent anaphylactic episodes.[23] None of the patients had skin lesions of UP. Two of the 5 patients in this series had baseline tryptase levels higher than 20 ng/mL, who, along with an additional patient who had a normal tryptase level, met the diagnostic criteria for systemic mastocytosis; whereas 2 patients had only 2 minor criteria that met the diagnosis of MMCAS. Alvarez-Twose et al[24] compared the clinical presentation of patients with ISM with or without skin lesions ($ISMs^+$ and $ISMs^-$, respectively) and those with nonclonal or idiopathic mast cell activation symptoms. Patients with $ISMs^-$ were more likely to have their episodes triggered by venoms, whereas drugs were the main provoking factor for patients with nonclonal and/or idiopathic mast cell activation disorders. Based on the findings, a clinical score termed REMA score (REMA is the abbreviation for Spanish Network of Mastocytosis), which takes into account the presence or absence of urticaria, sex, and tryptase levels was devised, and showed a high predictive value in determining the presence of clonal mast cell disease and, therefore, can be used to decide which patients would benefit from a bone marrow biopsy.[26] Another study, from the Netherlands, investigated whether urinary histamine metabolite levels could be used to predict the presence of mastocytosis in patients with mast cell activation symptoms.[39] In a cohort of 142 patients, none had mastocytosis when the baseline tryptase level was <10 ng/mL, and all had mastocytosis if the tryptase level was >43 ng/mL. For patients with tryptase levels between 10 and 43 ng/mL, urinary methylimidazole acetic acid and methylhistamine levels were higher for those with mastocytosis.

Several clinical and laboratory parameters exist to guide the clinician to assess the risk of systemic mastocytosis or a clonal mast cell disease in a patient who presents with mast cell activation symptoms and who does not have skin lesions of UP. These include the absence of urticaria and angioedema during the episodes, male sex, systemic reactions to Hymenoptera stings, elevated baseline tryptase levels, the presence of D816V c-kit mutation in peripheral blood, and elevated urinary histamine metabolites. The ultimate decision lies with the patient.

IDIOPATHIC SYSTEMIC MCAS

Some patients who present with systemic mast cell activation symptoms do not have any evidence of IgE-mediated disease or another explanation for secondary mast cell activation. If these patients do not have mastocytosis and their clinical presentation cannot be classified as idiopathic anaphylaxis, then idiopathic systemic MCAS can be considered as a possible diagnosis.[40] It is important to note that many other disorders can mimic mast cell activation symptoms and may even respond to medications used in treatment of mast cell activation symptoms. For example, *H pylori* infection, and irritable bowel syndrome are much more common diagnoses in the general population and can occur unrelatedly in patients with flushing due to other causes, such as autonomically or endocrine-mediated flushing or hypotension. A globus sensation or throat discomfort can be seen in patients with vocal cord dysfunction or irritable larynx syndrome. Some patients may report non−mast cell mediated drug intolerances as allergies, and some may have concerns with multiple food intolerances, despite the lack of evidence of an IgE-mediated mechanism. To that end, spicy foods are a well known trigger for nonspecific−mast cell activation; however, there is no strong evidence to prove histamine-releasing properties of other specific foods to suggest nonspecific mast cell activation. Some patients may have experienced an initial episode of anaphylaxis or mast cell activation, which may be followed by nonspecific symptoms attributed to mast cell activation. Therefore, it is important to document objective evidence of mast cell activation whenever possible before embarking on a therapy with medications that can potentially have toxicities. For example, visualization of the larynx during an acute episode or when obtaining tryptase levels provides objective evidence of these patients.

Diagnostic criteria were proposed and adopted by an international consensus group as an objective means to evaluate patients with MCAS.[5,13] According to these criteria, the patient must have symptoms of mast cell activation that involve 2 organ systems, must show a positive response to therapy that targets mast cell mediators, and must show an elevated level of a mast cell mediator during an episode. These criteria are most helpful for patients whose symptoms could not be evaluated or documented at the time of their reactions due to various reasons. Other causes of symptoms should be ruled out within reason and to the extent possible. Patients who show no clinical improvement with antihistamines, glucocorticoids, or epinephrine should be investigated for other etiologies. The most reliable surrogate marker of mast cell activation is tryptase.[32,41] The tryptase level should be obtained within 4 hours of an episode. An elevated tryptase value during a symptomatic episode is confirmatory of mast cell activation as the etiology of the symptoms. A meaningfully elevated tryptase level can be calculated according to the formula: baseline serum tryptase (bT) + 20% bT + 2 ng/mL.[13] Meaningful elevation cutoffs for urinary histamine metabolites or PGD2 or 11βPGF2-α (metabolite of PGD2) have not been established. To that end, there is lack of a complete understanding of other medical conditions and cellular sources associated with elevated urinary PGD2 and PGF2 levels, and, although these levels can be useful in selecting therapy with aspirin for those who can tolerate it, which relies on an elevated PGD2 and PGF2 level as the sole indicator of mast cell activation, should be approached with caution.[42]

Prospective large-scale studies are needed to validate the proposed criteria for MCAS. The largest case series evaluated 18 patients in a span of 3 years, which predated the proposed consensus criteria for mast cell activation, although patient selection criteria showed a significant overlap.[43] Patients were enrolled if they had at least 4 of the signs and symptoms of abdominal pain, diarrhea, flushing, dermographism, memory and concentration difficulties, or headache. None had evidence of mastocytosis or IgE-mediated allergies. In this series, the majority of patients had the constellation of dermographism, abdominal pain, and flushing, and all had detectable elevations in at least 1 mast cell mediator. Of the patients in the cohort, 67% had either a complete or major regression in symptoms while taking medications that target mast cell mediators. There was no significant difference in the numbers of intestinal mucosal mast cells between the patients and healthy control subjects. The genetic basis of MCAS is not known; however 1 study found familial clustering of cases.[44]

TREATMENT

All patients with systemic mast cell activation or a history of anaphylaxis should be prescribed multiple self-injectable epinephrine devices and be trained in their appropriate use.[45] Those who are allergic to Hymenoptera venom should be recommended VIT. Triggers of mast cell activation should be avoided. Empirical maintenance treatment directed against mast cell mediators is considered in all patients who present with recurrent mast cell activation symptoms. The response to therapy would also carry diagnostic implications, as stated above. We generally consider a stepwise approach to maintenance treatment of mast cell activation disorders. The first step includes an H1 antihistamine. Similar to management of chronic urticaria, H1 antihistamines may be prescribed up to 2 to 4 times of daily doses recommended for labeled indications. We generally prefer to start with a nonsedating antihistamine, which can be supplemented with a first-generation sedating antihistamine if nighttime symptoms are prominent or on an add-on as needed basis. The H2 antihistamines can be prescribed as a first-step therapy if gastrointestinal symptoms are prominent or can be added on together with a leukotriene blocking agent in the second step. The second step also involves a trial of oral cromolyn if gastrointestinal symptoms are prominent. Treatments beyond this step should be considered if there is strong suspicion or objective proof that the symptoms are attributable to mast cell activation. The third step includes consideration of systemic glucocorticoids. If the patient responds, then a slow taper over a few months should be attempted. Some patients require a small maintenance dose (<7.5 mg daily or every other day equivalent dose of prednisone). There is some evidence that patients with idiopathic anaphylaxis that requires higher maintenance doses of glucocorticoids may respond well to ketotifen, an H1 antihistamine with mast cell stabilizing properties, which is not available in oral form in the United States, with the exception of some compounding pharmacies.[46] The fourth step involves consideration of second-line agents shown to be effective in other disorders of mast cell activation. These may include drugs with efficacy in chronic spontaneous urticaria, such as hydroxychloroquine, dapsone, cyclosporine, and omalizumab. Randomized clinical trials on the efficacy of these agents in MCAS are lacking, and potential risks and benefits of these drugs should be considered carefully and discussed with the patient before initiation of therapy. Omalizumab has been reported to decrease the frequency of anaphylactic episodes in case reports of both clonal[47] and nonclonal mast cell activation disorders[48] and has also been used as a cotreatment to allow patients to receive VIT for those who had problems with systemic reactions during dose escalation or maintenance.[49] However, there are no placebo-controlled studies to recommend routine use of omalizumab at this time, especially when considering that the drug is not without adverse effects, is expensive, and is not US Food and Drug Administration approved for this indication. The fifth step applies to patients with mastocytosis (clonal mast cell disease) who have repeated life-threatening spontaneous anaphylactic episodes. These patients can be considered for mast cell cytoreductive therapies after careful discussion of risks and benefits. Alfa interferon and cladribine are the most commonly used mast cell cytoreductive agents.[50] Patient response to the various therapies shows a great variation. Some patients are easily controlled by first-line therapies, whereas others show resistance to multiple modalities. In the latter group of patients, the diagnosis of mast cell activation should be continually reevaluated and non−mast cell etiologies should be considered. For patients without objective evidence of mast cell activation, consideration should be given to discontinue all therapies beyond second line.

Finally, it should be emphasized that there is an unmet need for development of new therapies to control mast cell activation or counteract the effects of mast cell mediators. This will require a better understanding of mast cell mediator profiles released in different clinical scenarios as well as development of newer drugs that target mast cell activation. One study that evaluated the effects of various tyrosine kinase inhibitors showed that midostaurin inhibited IgE-mediated activation and dasatinib had a bimodal effect with enhancement of degranulation at lower concentrations.[51,52] Placebo-controlled randomized clinical trials with existing and investigational medications should be encouraged for patients with mast cell activation disorders to move beyond anecdotal reports and case series to establish evidence-based treatment recommendations.

REFERENCES

1. Galli SJ, Tsai M. Mast cells in allergy and infection: versatile effector and regulatory cells in innate and adaptive immunity. Eur J Immunol 2010;40:1843-51.
2. Gilfillan AM, Austin SJ, Metcalfe DD. Mast cell biology: introduction and overview. Adv Exp Med Biol 2011;716:2-12.
3. Castells M. Mast cell mediators in allergic inflammation and mastocytosis. Immunol Allergy Clin North Am 2006;26:465-85.
4. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.
5. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol 2010;126:1099-1104.e4.
6. Yell JA, Mbuagbaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosus. Br J Dermatol 1996;135:355-62.
7. Diogenes MJ, Diogenes PC, de Morais Carneiro RM, Neto CC, Duarte FB, Holanda RR. Cutaneous manifestations associated with antiphospholipid antibodies. Int J Dermatol 2004;43:632-7.
8. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. J Allergy Clin Immunol 2012;129:1307-13.
9. Wedi B, Raap U, Wieczorek D, Kapp A. Urticaria and infections. Allergy Asthma Clin Immunol 2009;5:10.
10. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part I.

Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol 2014;70:205.e1-205.e16. quiz 21-2.
11. Rubenstein M, Duvic M. Cutaneous manifestations of Hodgkin's disease. Int J Dermatol 2006;45:251-6.
12. Abonia JP, Blanchard C, Butz BB, Rainey HF, Collins MH, Stringer K, et al. Involvement of mast cells in eosinophilic esophagitis. J Allergy Clin Immunol 2010;126:140-9.
13. 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.
14. Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 2001;25:603-25.
15. Horny HP, Metcalfe DD, Bennett JM, Bain BJ, Akin C, Escribano L, et al. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: IARC Press; 2008. p. 54-63.
16. Metcalfe DD. Mast cells and mastocytosis. Blood 2008;112:946-56.
17. Bodemer C, Hermine O, Palmerini F, Yang Y, Grandpeix-Guyodo C, Leventhal PS, et al. Pediatric mastocytosis is a clonal disease associated with D816V and other activating c-KIT mutations. J Invest Dermatol 2010;130:804-15.
18. Kristensen T, Vestergaard H, Bindslev-Jensen C, Moller MB, Broesby-Olsen S. Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis. Am J Hematol 2014. doi: 10.1002/ajh.23672. [Epub ahead of print].
19. Akin C. Multilineage hematopoietic involvement in systemic mastocytosis. Leuk Res 2003;27:877-8.
20. Teodosio C, Garcia-Montero AC, Jara-Acevedo M, Alvarez-Twose I, Sanchez-Munoz L, Almeida J, et al. An immature immunophenotype of bone marrow mast cells predicts for multilineage D816V KIT mutation in systemic mastocytosis. Leukemia 2012;26:951-8.
21. Hartmann K, Henz BM. Cutaneous mastocytosis: clinical heterogeneity. Int Arch Allergy Immunol 2002;127:143-6.
22. Wolff K, Komar M, Petzelbauer P. Clinical and histopathological aspects of cutaneous mastocytosis. Leuk Res 2001;25:519-28.
23. 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.
24. Alvarez-Twose I, Gonzalez de Olano D, Sanchez-Munoz L, Matito A, Esteban-Lopez 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.
25. Schwartz LB, Irani AM. Serum tryptase and the laboratory diagnosis of systemic mastocytosis. Hematol Oncol Clin North Am 2000;14:641-57.
26. Alvarez-Twose I, Gonzalez-de-Olano D, Sanchez-Munoz 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.
27. Valent P, Aberer E, Beham-Schmid C, Fellinger C, Fuchs W, Gleixner KV, et al. Guidelines and diagnostic algorithm for patients with suspected systemic mastocytosis: a proposal of the Austrian competence network (AUCNM). Am J Blood Res 2013;3:174-80.
28. Sperr WR, El-Samahi A, Kundi M, Girschikofsky M, Winkler S, Lutz D, et al. Elevated tryptase levels selectively cluster in myeloid neoplasms: a novel diagnostic approach and screen marker in clinical haematology. Eur J Clin Invest 2009;39:914-23.
29. Siles R, Xu M, Hsieh FH. The utility of serum tryptase as a marker in chronic spontaneous urticaria. Acta Derm Venereol 2013;93:354-5.
30. Ferrer M, Nunez-Cordoba JM, Luquin E, Grattan CE, De la Borbolla JM, Sanz ML, et al. Serum total tryptase levels are increased in patients with active chronic urticaria. Clin Exp Allergy 2010;40:1760-6.
31. Dugas-Breit S, Schopf P, Dugas M, Schiffl H, Rueff F, Przybilla B. Baseline serum levels of mast cell tryptase are raised in hemodialysis patients and associated with severity of pruritus. J Dtsch Dermatol Ges 2005;3:343-7.
32. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunol Allergy Clin North Am 2006;26:451-63.
33. Castells M, Metcalfe DD, Escribano L. Diagnosis and treatment of cutaneous mastocytosis in children: practical recommendations. Am J Clin Dermatol 2011;12:259-70.
34. Bonadonna P, Perbellini O, Passalacqua G, Caruso B, Colarossi S, Dal Fior D, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. J Allergy Clin Immunol 2009;123:680-6.
35. Oude Elberink JN, de Monchy JG, Kors JW, van Doormaal JJ, Dubois AE. Fatal anaphylaxis after a yellow jacket sting, despite venom immunotherapy, in two patients with mastocytosis. J Allergy Clin Immunol 1997;99:153-4.
36. Rueff F, Przybilla B, Bilo MB, Muller U, Scheipl F, Aberer W, et al. Predictors of side effects during the buildup phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. J Allergy Clin Immunol 2010;126:105-111.e5.
37. Rueff F, Vos B, Elberink JO, Bender A, Chatelain R, Dugas-Breit S, et al. Predictors of clinical effectiveness of Hymenoptera venom immunotherapy. Clin Exp Allergy 2014. doi: 10.1111/cea.12275. [Epub ahead of print].
38. Bridgman DE, Clarke R, Sadleir PH, Stedmon JJ, Platt P. Systemic mastocytosis presenting as intraoperative anaphylaxis with atypical features: a report of two cases. Anaesth Intensive Care 2013;41:116-21.
39. van Doormaal JJ, van der Veer E, van Voorst Vader PC, Kluin PM, Mulder AB, van der Heide S, et al. Tryptase and histamine metabolites as diagnostic indicators of indolent systemic mastocytosis without skin lesions. Allergy 2012;67:683-90.
40. Lee MJ, Akin C. Mast cell activation syndromes. Ann Allergy Asthma Immunol 2013;111:5-8.
41. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. N Engl J Med 1987;316:1622-6.
42. Butterfield JH, Weiler CR. Prevention of mast cell activation disorder-associated clinical sequelae of excessive prostaglandin D(2) production. Int Arch Allergy Immunol 2008;147:338-43.
43. 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.
44. Molderings GJ, Haenisch B, Bogdanow M, Fimmers R, Nothen MM. Familial occurrence of systemic mast cell activation disease. PLoS One 2013;8:e76241.
45. Cardet JC, Akin C, Lee MJ. Mastocytosis: update on pharmacotherapy and future directions. Expert Opin Pharmacother 2013;14:2033-45.
46. Ditto AM, Harris KE, Krasnick J, Miller MA, Patterson R. Idiopathic anaphylaxis: a series of 335 cases. Ann Allergy Asthma Immunol 1996;77:285-91.
47. Carter MC, Robyn JA, Bressler PB, Walker JC, Shapiro GG, Metcalfe DD. Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis. J Allergy Clin Immunol 2007;119:1550-1.
48. Bell MC, Jackson DJ. Prevention of anaphylaxis related to mast cell activation syndrome with omalizumab. Ann Allergy Asthma Immunol 2012;108:383-4.
49. Kontou-Fili K, Filis CI. Prolonged high-dose omalizumab is required to control reactions to venom immunotherapy in mastocytosis. Allergy 2009;64:1384-5.
50. Valent P, Sperr WR, Akin C. How I treat patients with advanced systemic mastocytosis. Blood 2010;116:5812-7.
51. Krauth MT, Mirkina I, Herrmann H, Baumgartner C, Kneidinger M, Valent P. Midostaurin (PKC412) inhibits immunoglobulin E-dependent activation and mediator release in human blood basophils and mast cells. Clin Exp Allergy 2009;39:1711-20.
52. Kneidinger M, Schmidt U, Rix U, Gleixner KV, Vales A, Baumgartner C, et al. The effects of dasatinib on IgE receptor-dependent activation and histamine release in human basophils. Blood 2008;111:3097-107.

J ALLERGY CLIN IMMUNOL PRACT
MAY/JUNE 2014

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: May 2014. Credit may be obtained for these courses until June 30, 2015.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates these educational activities for a maximum of 1 AMA PRA Category 1 Credit. Physicians should only claim credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Cem Akin, MD, PhD

Activity Objectives

1. To know the pathologic markers of mast cell clonality in patients with mast cell activation disorders.
2. To recognize clinical scenarios that are more likely to be associated with mastocytosis in patients with a history of anaphylaxis or mast cell activation symptoms

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: C. Akin has received consultancy fees from Novartis and Patara Pharma; has received research support from Dyax; and has a patent for an LAD2 cell line with the National Institutes of Health.