

Mast cell disorders and idiopathic anaphylaxis: Evaluation and management

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ABSTRACT

Background: Our understanding of mast cell activation disorders continues to grow, and our management of these syndromes is improving with this increase in knowledge. Despite these advances, there remain some areas of confusion.

Conclusion: In this article, we discussed these areas and offered thoughts about establishing the diagnosis and management.

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The first mention of anaphylactic episodes of unknown cause came from Bacal *et al.*¹ in 1978. Bacal *et al.*¹ reported 21 patients with life-threatening manifestations, some of whom defied efforts to identify the etiologic agent. Initially, the concept of an anaphylactic reaction without an allergen was somewhat of a paradox. However, shortly thereafter other reports came forth,^{2,3} and the concept became established in our lexicon of allergy terms.⁴

The first mention of the term mast cell activation disorder (MCAD) was somewhat harder to find. The first reference that we could identify seemed not to be in an allergy/immunology journal but in *Hypertension* in 2005. The article was written by cardiologists and was entitled, “Hyperadrenergic postural tachycardia syndrome [POTS]: a mast cell activation disorder.”⁵ The authors wrote, “Here we describe POTS patients with MCAD ... diagnosed by episodes of flushing and abnormal increases in urine methylhistamine.”⁵ The early roots of MCADs that cause systemic manifestations can be traced to even earlier observations.⁶

Just as the concept of anaphylaxis without an identifiable allergen was initially difficult to accept, the introduction of MCADs has been just as puzzling to the allergist. Perhaps the reason for this is that the initial descriptions, as mentioned, were in the nonallergy literature. It is not surprising, therefore, that, in a recent issue of one of our allergy journals devoted to

anaphylaxis and MCADs, the editor of this issue, Golden,⁷ stated, “The analogy of mast cell disorders with a ‘house of mirrors’ is quite apt. It seems everywhere we look we see mast cell disorders, things that look like mast cell disorders, and a reflection of mast cell disorders, but not all of them are what they seem, and we see things we cannot yet explain.” Golden was not only referring to the terminology about these MCADs in general but specifically to the seven papers in this issue that deal with anaphylaxis and other mast cell disorders that he edited.^{8–14}

Perhaps contributing to the confusion is the terminology used in *The International Classification of Diseases, Tenth Revision* to refer to mast cell disorders:

Mast cell activation syndrome and related disorders, D89.4

Mast cell activation unspecified, D89.40

Monoclonal activation syndrome, D89.41

Idiopathic mast cell activation syndrome, D89.42

Other mast cell activation disorder, D89.49

Secondary mast cell activation, D89.43

No doubt adding to the confusion so eloquently described by Golden⁷ is perhaps the fact that the most iconic article that refers to MCADs was published in a hematology journal, *Blood*, and not in an allergy/immunology journal, in 2007.¹⁶ In this article, Akin *et al.*¹⁶ described 12 patients who presented with idiopathic anaphylaxis. These patients, for lack of a better term, could be said to have a “forme fruste” of systemic mastocytosis. None satisfied the classic bone marrow biopsy criteria required to establish a diagnosis of systemic mastocytosis; however, five had evidence of one or more minor criteria for this condition, and three had the activating mutation of tyrosine kinase KIT gene (*KIT*) (D816V).¹⁶

The article was entitled “Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with ‘idiopathic’ anaphylaxis.”¹⁶ For the first time, it was shown that patients who presented with idiopathic anaphylaxis might have a condition

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that could respond to inhibitors that target a mutated *KIT*. In 2010, perhaps the first publication designed to classify patients who present with “a mast cell activating syndrome” was proposed.¹⁷ The schemata suggested in this, as seen in the article entitled, “Mast cell activation syndrome: proposed diagnostic criteria,” introduced the criteria classification scheme (primary, secondary, and idiopathic), which has since been used by numerous other publications.¹⁷

It was about the same time when a publication in an allergy journal introduced the term “clonal mast cell disorders”.¹⁸ In this article, Alvarez-Twose *et al.*¹⁸ wanted to analyze the clinical, biologic, and molecular characteristics of adult patients who presented with systemic mast cell activation symptoms, including anaphylaxis, in the absence of cutaneous mastocytosis. They evaluated 83 patients who presented with what they termed “mast cell activation symptoms.”¹⁸ They did bone marrow examinations to evaluate the presence of clonality. There were two major clonal groups, one group that met World Health Organization diagnostic criteria for mastocytosis (51 subjects)¹⁹ and the other group that did not meet the criteria (3 subjects), of the total 83 patients who were evaluated.¹⁸ This left 32 patients of the 83 who showed no evidence of a clonal disorder. The researchers used the term, “nonclonal mast cell activation disorder” to refer to these 32 patients.¹⁸ In addition, these researchers looked at the clinical characteristics of the clonal and nonclonal groups.

Shortly thereafter, Hamilton *et al.*²⁰ published an article entitled “Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations” in 2011. This was the second article that used the terminology surrounding MCAD that appeared in our allergy literature. The patients described in this article expressed clinical features somewhat different than those noted in the aforementioned reports. These included headache, memory and concentration difficulties, and dermatographism.²⁰ In this group, 94% of the patients had abdominal pain.²⁰ Also, some patients presented to the gastroenterologist with unexplained gastrointestinal symptoms (bloating, flushing, irritable bowel syndrome and diarrhea, or diarrhea plus constipation); all the patients had at least one elevated mast cell mediator, and 67% responded to medications (such as antihistamines) that target mast cell mediators.²⁰ Curiously, in this group there was no significant difference in the number of intestinal mucosal mast cells between the patients and the healthy subjects.²⁰

When looking at the literature as a whole as it existed in 2011, it was obvious that confusion existed as to the definition of MCADs and especially as to the place of idiopathic anaphylaxis within the framework of that definition. In addition to the difficulties encountered in terminology and classification, a second

problem was beginning to arise with regard to the nature of MCADs in general. That is, confusion existed as to what were the innate clinical manifestations that identified groups of patients with mast cell activation syndromes. A number of patients were beginning to present in the offices of physicians caring for these patients. They had symptoms other than those typically encountered by allergists/immunologists as being related to anaphylactic and acute immediate hypersensitivity disorders.

Such symptoms as described later in the medical literature^{21,22} included fatigue, fibromyalgia-type pain, paresthesias, chills, and cognitive dysfunction. The contention that MCADs can cause these types of symptoms has also been popularized by a book presumably written, at least in part, for the lay public. It was entitled, *Never Bet Against Occam: Mast Cell Activation Disease and the Modern Epidemics of Chronic Illness and Medical Complexity* “by Afrin.”²² Afrin²¹ was also the lead author in the *American Journal of Medical Science* article cited above. An online description of the book states that patients gain some degree of consolation that “comes from finally having a unifying diagnosis other than ‘psychosomatism’.”

These types of symptoms were also being mentioned by patients, as later described in a report by the Mastocytosis Society. It was entitled “The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions.”²³ This report evaluated patients’ perception of their disease. These patients included those diagnosed with cutaneous mastocytosis, systemic mastocytosis, mast cell activation syndrome, and idiopathic anaphylaxis, and a small group of “other” subjects and some with “diagnosis not determined or provided.”²³ Four hundred and twenty participants were initially included. These patients exhibited classic manifestations of mast cell release, including anaphylaxis, flushing, and wheezing; however, other less “classic” symptoms not typically associated with mast cell degranulation, including anxiety, depression, and brain fog, were mentioned in significant numbers.²³ These are presented in Table 1.

Thus, at this point in time, there was confusion in several areas as follows:

1. What manifestations were required to make a diagnosis of an MCAD? Specifically, could one do so based on symptoms such as those seen in Table 1?
2. Where did idiopathic anaphylaxis and allergen-induced anaphylaxis fit into the classification of MCADs? Specifically, what is the difference between nonclonal mast cell activation syndrome and idiopathic anaphylaxis, and the difference between systemic mastocytosis and clonal MCAD?

Table 1 “Nonclassic” symptoms of mast cell activation disorders that appear in the Mastocytosis Society survey on these disorders*

Symptom	No. (%)
Joint manifestations	258 (61.4)
Muscle nerve connective tissue	210 (50.0)
Fatigue	320 (76.2)
Headache	267 (63.6)
Brain fog and/or cognitive difficulties	281 (66.9)
Weakness	225 (53.6)
Anxiety	255 (60.7)
Depression	207 (49.3)

*Modified from Ref. 22.

The major object of this discussion was to deal with these questions in hopes to clarify diagnostic and management issues for the allergist/immunologist in the daily practice of our discipline.

CLARIFICATIONS OF CLASSIFICATION ISSUES

In response to the conundrums and confusion noted above, in 2012, a multispecialty group of individuals interested in mast cell disorders was convened in Vienna, Austria. One of the missions of this group was to address and clarify what diagnostic criteria should be used to make the diagnosis of an MCAD and to classify such disorders, as in, classify mast cell activation disorders (MCAD) and similar disorders including idiopathic anaphylaxis. This group published a position paper in the *International Archives of Allergy and Immunology* entitled “Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal.”²⁴

Twenty physicians were on this panel. They represented several different countries and multiple disciplines, including hematology/oncology, gastroenterology dermatology, and allergy/immunology. From their deliberations, several consensus conclusions were made, not the least of which was what symptoms occurred in patients with MCADs.²⁴ Their conclusions are seen in Table 2. It is clear that the list of symptoms does not include several symptoms noted in the article published under the aegis of the Mastocytosis Society and were absent a number of manifestations thought to be characteristic as described by Afrin *et al.*^{21,22} In addition, poor concentration and memory, manifestations noted in Hamilton *et al.*²⁰ were not mentioned. The second major contribution by the consensus panel was a definition of the requirements for a diagnosis of mast cell activation syndrome summarized in Table 3.

Table 2 Symptoms considered typical for mast cell activation disorders: a consensus proposal*

Symptom	Members Who Agree on the Presence of the Symptom, %
Flushing	95
Pruritus	90
Urticaria	85
Angioedema	75
Nasal congestion	90
Nasal pruritus	90
Wheezing	70
Throat swelling	85
Headache	90
Hypotension	95
Diarrhea	90

*Modified from Ref. 23.

This consensus panel also suggested a mechanistic classification of MCADs as follows²⁴:

1. Primary (clonal)
 - A. Systemic mastocytosis
 - B. Monoclonal mast cell activation syndrome
2. Secondary (nonclonal)
 - A. Allergic disorders
 - B. Chronic inflammatory and neoplastic disorders
 - C. Physical urticaria
 - D. Chronic autoimmune urticaria
3. Idiopathic
 - A. Anaphylaxis
 - B. Urticaria and/or angioedema
 - C. Mast cell activation syndrome.

Despite this eloquently written and intensively researched consensus report,²³ ostensibly there still remains difficulty in establishing the diagnosis of MCADs in the clinic. This is evident by a more recent letter to the editor composed of many of the same members who participated in the 2012 consensus document.²⁵ In this letter, the authors state, “Referrals to centers with experience in treatment of mast cell disorders with a diagnosis of mast cell activation syndrome have increased dramatically recently. The patients referred often do not meet the definition of mast cell activation syndrome and have often undergone extensive evaluations. Referral centers frequently find that, in the face of these extensive previous evaluations and in the absence of evidence that mast cells are involved, they have little to offer. This letter was written to summarize this situation and to propose a way forward.”²⁵ Thus, it is clear, especially for the practicing allergist/immunologist that some issues remain unresolved and continue to “muddy the

Table 3 Proposed criteria for the definition of a mast cell activation syndrome*

A mast cell activation syndrome is a specific syndrome with systemic mast cell activation that is usually severe and can be clonal (primary), nonclonal (secondary), or idiopathic. The following three criterion are needed to make a diagnosis:	
(A)	Recurrent episodic symptoms consistent with mast cell activation in at least two organ systems; these include skin, gastrointestinal, cardiovascular, respiratory, nasal, ocular
(B)	A positive response to treatment with medications targeting mast cell mediators, <i>e.g.</i> , H ₁ - and H ₂ -antagonists, cromolyn sodium
(C)	Documented biochemical evidence of mast cell activation, such as an elevated level of tryptase (preferred) and urinary histamine metabolites, or prostaglandin levels

*Modified from Ref. 8.

Table 4 World Health Organization biopsy criteria for a systemic mastocytosis diagnosis requires 1 major and 1 minor, or 3 minor criteria*

Major criterion	Multifocal accumulation of compact clusters of ≥ 15 mast cells in the bone marrow or another organ
Minor criteria	A. Mast cell infiltrates in the bone marrow or other extracutaneous organ showing $>25\%$ of mast cells spindle-shaped or atypical in the bone marrow B. The presence of activating <i>KIT</i> mutation at codon D816 in the bone marrow, blood, or extracellular organ C. <i>KIT</i> + mast cells in the bone marrow, blood, or other extracutaneous organ(s) expressing CD25 with or without CD2 D. Serum total tryptase concentration of equal to or greater than 20 ng/mL

KIT = tyrosine kinase *KIT* gene.

*Modified from Ref. 42.

waters,” which makes the diagnosis puzzling and, therefore, treatment indecisive.

As mentioned above, from a clinical standpoint, the perception of the differences between monoclonal mast cell activation syndrome and idiopathic systemic anaphylaxis, and the differences between nonclonal mast cell activation syndrome and idiopathic anaphylaxis remain problematic. It is important, therefore, to address these still somewhat difficult-to-define subcategories of MCADs. In addition, as discussed below, the frequency of “nonclassic” manifestations has not been totally clarified.

MONOCLONAL MAST CELL ACTIVATION SYNDROME VERSUS SYSTEMIC MASTOCYTOSIS

Systemic mastocytosis is, in actuality, a biopsy diagnosis and to be certain of this diagnosis, biopsy criteria

must be met. The World Health Organization criteria for the diagnosis of systemic mastocytosis^{26,27} is seen in Table 4. In monoclonal mast cell activation syndrome, as mentioned, these biopsy criteria are not met. Marrow biopsy specimens may show sparse infiltrates of mast cells not in clusters and the mast cell burden will be lower than that seen in mastocytosis. Mast cells may be bi-phenotypic for CD25 expression. Basal serum tryptase concentration can be elevated but usually does not exceed 20 ng/mL in monoclonal mast cell activation syndrome. *D816V KIT* mutation is usually confined to a subpopulation of mast cells and does not involve all of those seen. Usually monoclonal mast cell activation syndrome is a disorder of activation rather than proliferation. Usually it does not progress to systemic mastocytosis, but, apparently, some cases can do so.¹⁰ Thus, physicians need to reassess their provisional diagnosis over time.

More puzzling, however, is the distinction between mast cell activation syndrome, which is not clonal, and idiopathic anaphylaxis. Perhaps the best way to distinguish these two entities is that, in idiopathic anaphylaxis, a survey of the literature does not reveal chronic symptoms of abdominal pain, poor concentration and memory, fatigue, chronic gastrointestinal symptoms, anxiety, and depression. In idiopathic anaphylaxis, patients are usually absent any manifestations of chronic disease related to the anaphylactic episodes. Whereas, as noted above, with nonclonal mast cell activation syndrome, varying degrees of these chronic symptoms have been reported, and they are present unrelated to episodes of anaphylaxis. It is important to note that the subpopulation identified as “nonclonal” may, in fact, be clonal. However, due to the lack of technology in this area, the clonality has not yet been discovered. Also, in patients who present with a possible diagnosis of idiopathic anaphylaxis, an elevated basal serum tryptase should change the working diagnosis toward a mast cell disorder. Patients with mast cell disorders more commonly experience syncope or near syncope, flushing, tachycardia, and diarrhea but not urticaria.

AN UNEXPECTED OCCURRENCE

Amid this somewhat murky discussion about what can constitute an MCAD arose an unexpected finding, which perhaps has complicated the situation further.^{28–34} This interesting discovery was made by Lyons *et al.*²⁸ and published in 2014. The researchers discovered a Mendelian inheritance of elevated serum tryptase (*International Classification of Diseases, Tenth Revision* code R74.8),¹⁵ which was associated with atopy and connective tissue abnormalities. They found a few families with dominantly inherited elevated levels of tryptase and coined the term “familial hypertryptasemia.”²⁸ They found that patients in these families not only had hypertryptasemia but also complex clinical features, some of which may have been related to mast cell activation.²⁸ This discovery occurred in nine subjects with atopy originally referred to the National Institute of Allergy and Infectious Disease for evaluation of severe allergic skin, airway, gastrointestinal disease, or systemic mastocytosis.²⁸ All of these subjects had elevated baseline tryptase levels, and there was a dominant inheritance pattern associated with symptoms consistent with mast cell mediator release and additional nonatopic features.²⁸

Manifestations included episodic flushing; urticaria; pruritus; gastrointestinal symptoms, including cramping abdominal pain and diarrhea; chronic musculoskeletal pain; and also a hypermobile connective tissue phenotype. In this group of patients, the mean basal serum tryptase levels in a resting state was 21.6 ± 1.4 ng/mL. Symptoms could occur spontaneously or they could be triggered by heat, exercise, vibration, emotional stress, or minor physical trauma. A history of anaphylaxis was reported in 10 of 33 subjects from six different families. The anaphylaxis could be idiopathic or related to exposure to foods or to insect stings. All of the subjects had atopic manifestations. Of particular interest in this group of patients was the presence of autonomic dysfunction, which manifested as POTS. This was reported in 10 of the subjects. Also, a neuropsychiatric diagnosis was present in 17.²⁸ The finding of POTS harkens back to our mention above of the first notation of mast cell activation disease in the literature.⁵

In this group of subjects, each of the five clusters of clinical characteristics (skin, gastrointestinal, atopic, connective tissue, and neuropsychiatric) were indicative of and significantly associated with increased tryptase levels. Also, of note is that none of the subjects who were biopsied met the World Health Organization established criteria for a diagnosis of systemic mastocytosis or monoclonal mast cell activation syndrome by biopsy.²⁸

Within a few months, a second report by the same group appeared.³⁰ It described three generations of a family with four affected relatives who had experienced

Table 5 Clinical features observed in hereditary alpha-tryptasemia*

Clinical Features	Patients, % range
Basal serum tryptase level > 8 ng/mL	100
Chronic gastroesophageal reflux symptoms	56–77
Arthralgia	44–45
Body pains and/or headache	33–47
Flushing, itching	32–55
Irritable bowel syndrome	28–49
Sleep disturbance	32–39
Systemic immediate hypersensitivity reactions	21–28
Retained primary dentition	20–33
Systemic venom reaction	14–22
Congenital skeletal abnormality	11–26
Joint hypermobility	0–28
Positive Tilt table test result	0–11

*Modified from Ref. 32.

recurrent abdominal pain and diarrhea for several years. One had a basal serum tryptase of 29 ng/mL and an increase of >20% plus 2 ng/mL recorded repeatedly at the time of symptoms.³⁰ One family member in this group had a *D816V KIT* mutation. Improvement occurred with oral cromolyn and H₁- and H₂-antagonists. A diagnosis of monoclonal activation syndrome was made.³⁰ In the second group of patients, symptoms were more typical for mast cell activation syndrome, although most of the symptoms were limited to the gastrointestinal tract.³⁰ Of note in this report is that serial elevations of tryptase levels over time correlated with the presence and severity of abdominal symptoms, including cramps and diarrhea. Ehlers Danlos-hypermobility has also been reported in association with Mast Cell Activation Syndrome (MCAS) and POTS.^{33,34}

Approximately 2 years after these index reports, the underlying pathogenesis of familial hypertryptasemia was discovered.²⁸ It was found that affected individuals had duplications or triplications of the Tryptase Alpha/Beta 1 (*TPSAB1*) gene that encodes alpha-tryptase. In this article, they also note that individuals with three copies of this gene had higher basal serum levels of tryptase and were more symptomatic than those who had only two copies.²⁸ This suggested a gene-dose effect. They reconfirmed that these duplications in *TPSAB1* were associated with irritable bowel syndrome, cutaneous symptoms, connective tissue abnormalities, and dysautonomia as well as more typical symptoms of mast cell activation. A clinically oriented review by Lyons³² of

Table 6 Diagnostic tests to consider in a patient presenting with a possible MCAD

Patient with Mostly Flushing and Abdominal Symptoms	Anaphylaxis	POTS-like symptoms	Alpha hypertryptasemia
Chromogranin A	Basal serum tryptase Skin tests to foods or to drugs when indicated	Basal serum tryptase Refer for Tilt test	Basal serum tryptase Test for <i>TPSAB1</i> gene
Vasointestinal polypeptides, such as neurokinin A, substance P, pancreastatin 5-HIAA	a. Skin tests by using standard commercially available extracts; b. Skin tests by using fresh food		
Octreotide-assisted imaging	Serum-specific IgE to foods and drugs when indicated; consider a diagnostic-therapeutic trial with prednisone; oral challenge; Serum anti-alpha-gal (Galactose-alpha-1,3-galactose) IgE; baseline and during anaphylaxis serum tryptase; baseline and during anaphylaxis 24-hr urinary histamine metabolites; prostaglandin D ₂ (urine or plasma or urinary metabolite 9 α , 11 β -prostaglandin F ₂); peripheral blood <i>c-KIT</i> mutation for codon D816V; bone marrow biopsy		

MCAD = Mast cell activation disorders; POTS = postural tachycardia syndrome; TPSAB1 = Tryptase Alpha/Beta 1; 5- HIAA = 5- Hydroxyindoleacetic acid; IgE = immunoglobulin E; c-KIT = tyrosine kinase receptor.

hereditary alpha-tryptasemia, which highlights the manifestations of patients with this disorder was published in 2018. A summary of the clinical features discussed in this review is seen in Table 5.

In summary, hereditary alpha-hypertryptasemia seems to be not uncommon. Individuals with this trait can present with a complex group of symptoms, including those who suggest an MCAD. There is an apparent gene-dose relationship between the number of copies of the alpha-tryptase gene, the presence of elevated serum tryptase, and the degree of symptoms. The discovery of “nonclassic” symptoms in these individuals has perhaps further complicated the perception as to what manifestations may occur in MCADs.

It should be noted that questions still surround the significance of these reports of patients with hereditary alpha-tryptasemia. The number of patients reported is small. Clinical findings in patients with this syndrome have yet to be confirmed by an independent, unselected, and larger cohort. It also should be

noted that individuals with the phenotype may be asymptomatic. Also, the phenotype itself can be expressed by 6% of the population. Thus, this syndrome could possibly, at this time, best be described as a genetic variant of unknown significance. Finally, a test for alpha-hypertryptasemia can be obtained at the web site Gene By Gene (Gene By Gene, Houston, Texas).³⁵

APPROACH TO THE PATIENT WITH IDIOPATHIC ANAPHYLAXIS AND/OR SUGGESTIONS OF AN MCAD

There have been many well thought out and deliberative attempts to standardize and simplify the approach to a patient with a possible MCAD. More than one algorithm and strategic approach has been published.^{36–40} However, the complexities of these approaches have recently grown with the controversies involved in determining the clinical manifestations of

MCADs and the discovery of patients with alpha-hypertryptasemia.

Akin³⁸ attempted to clarify the relationship between idiopathic anaphylaxis as a precursor of mast cell activation syndrome. He also discussed whether mast cell activation syndrome can present with chronic rather than only acute episodes of idiopathic anaphylaxis and discusses the controversy that involves the relationship between mast cell activation syndrome and POTS and connective tissue disorders.³⁸

Patients may approach the allergist in regard to the diagnosis of a mast cell activation syndrome in four distinct ways:

1. They may present with nontypical symptoms, perhaps after reading material online about MCADs. These patients may present with the statement, "I have a mast cell activation disorder." However, not infrequently, the symptoms experienced cannot be proven to be due to mast cell activation.
2. Patients may present with symptoms suggestive of mast cell activation, such as flush and abdominal symptoms but may have another condition such as carcinoid or another type of polypeptide-secreting tumor.
3. Patients can present with symptoms suggestive of POTS and/or alpha hypertryptasemia.
4. The most common presentation is probably patients who present with classic idiopathic anaphylaxis.

The treatment will vary, dependent on the actual diagnosis. The diagnostic measures, depending on the symptoms, may include those suggested for the workup of idiopathic anaphylaxis, which can be fortified by adding tests for alpha-hypertryptasemia, carcinoid, or another type of vasointestinal-polypeptide tumor, and/or POTS syndrome (Table 6).

If a patient seems to have a true MCAD (either systemic mastocytosis, monoclonal mast cell activation syndrome, mast cell activation syndrome, or idiopathic anaphylaxis), the decision as to whether to do a bone marrow biopsy should be entertained. Greenberger and Metcalfe¹⁰ dealt with this issue and suggested that a bone marrow biopsy can be indicated for the following reasons:

1. Secure the diagnosis of systemic mastocytosis
2. Identify whether a patient with a serum tryptase level of ≥ 15 ng/mL has systemic mastocytosis, monoclonal mast cell activation syndrome, or, perhaps, familial hypertryptasemia
3. Determine whether urticaria pigmentosa in an adult patient is associated with an underlying idiopathic systemic mastocytosis
4. Explore whether patients with a working diagnosis of idiopathic anaphylaxis, mast cell

activation syndrome, or symptoms of mast cell activation have undiagnosed idiopathic systemic mastocytosis

5. Exclude systemic mastocytosis in a patient who has survived an anaphylactic reaction to a Hymenoptera sting and has a baseline serum tryptase level of >11.4 ng/mL. This is especially true if that patient has negative skin test results and serum-specific immunoglobulin E to Hymenoptera venoms.

Clearly, most patients with mastocytosis who have experienced insect anaphylaxis will have concurrent venom allergy detected by serum-specific immunoglobulin E or skin testing. It is rare for these patients to have a negative skin or serum test result.

There have been attempts to assist the clinician further in deciding when to do a bone marrow biopsy. Of particular note in this regard is an article by Carter *et al.*³⁹ The objectives of this article were threefold:

1. To determine the prevalence of clonal mast cell disorders among patients with idiopathic anaphylaxis
2. To establish criteria to identify those patients who require a bone marrow biopsy
3. To discern whether the pathogenesis of idiopathic anaphylaxis involves a hyperresponsive mast cell compartment.

They found that clonal mast cell disease was diagnosed in 14% of their subjects. The blood mutation analysis for *D816V KIT* was useful in identifying those who did have systemic mastocytosis but not in those with monoclonal mast cell activation syndrome. They had findings consistent with those of Alvarez-Twose *et al.*¹⁸ in that there are certain characteristics that distinguish systemic mastocytosis from nonclonal disease, which thus suggests that a bone marrow biopsy is indicated.³⁹ These include the following:

1. A baseline tryptase level >20 ng/mL
2. Cardiovascular symptoms versus cutaneous symptoms
3. Male gender
4. Insect anaphylaxis with a baseline tryptase level >11 ng/mL
5. A positive *D816V KIT* mutation analysis in blood.

Treatment will be dependent solely on the diagnosis. The preventive treatment of idiopathic anaphylaxis has been discussed in detail elsewhere.⁴ A number of drugs or classes of drugs that have been used is seen in Table 7. In the case of systemic mastocytosis, tyrosine kinase inhibitors have been used. They have included, *e.g.*, imatinib, dasatinib, midostaurin. At this time, treatment with tyrosine kinase inhibitors is currently approved only for patients with advanced systemic mastocytosis (usually those with hematologic problems). Imatinib and dasatinib

Table 7 Preventive treatments that have been suggested for therapy of idiopathic anaphylaxis

1. Anti-mediator drugs (*e.g.*, H₁- and H₂-antagonists, antileukotrienes)
2. Mast cell stabilizing agents (cromolyn sodium, poor systemic absorption, and usually not effective in preventing systemic symptoms)
3. Combination mast cell stabilizing agents and anti-histamine (*e.g.*, ketotifen)
4. Prednisone
5. Omalizumab
6. "Antimetabolites"
 - a. Cyclosporin/tacrolimus
 - b. Mycophenolate mofetil
 - c. Methotrexate
 - d. Azathioprine

are not effective in most patients. Although, rare, idiopathic anaphylaxis can be fatal, the vast majority of patients are managed successfully, although not without recurrences, by the agents in Table 7. In the rare instance when one is faced with a person who has symptoms related to both mast cell activation and POTS syndrome, treatment should be directed against the POTS syndrome in addition to the management of mast cell activation symptoms.

For symptoms related to POTS, the patient should be referred to a specialist interested in this syndrome. There are relatively few centers equipped to diagnose POTS. For allergists unfamiliar with a local resource, the Dysautonomia Support Network is a resource for locations of centers that deal with POTS.⁴¹ This organization has a board of directors that consists of physicians in various areas of the country who manage patients with POTS. The treatment of alpha hypertryptasemia is based directly on the manifestations in a given patient and will, most likely, in most instances require the help of other specialists. It is important to note that hereditary alpha-tryptasemia has not been established as a "distinct disease" and has no specific treatment. Symptoms of concomitant disease can be treated individually.

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