Mast Cell Activation Syndromes Presenting as Anaphylaxis

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KEYWORDS

• Anaphylaxis • Mastocytosis • Mast cell activation syndrome • Mast cells • Tryptase

KEY POINTS

- Clonal mast cell disease should be suspected in patients presenting with recurrent hypotensive syncopal or near-syncopal episodes without urticaria or angioedema.
- Patients with severe systemic reactions to hymenoptera and elevated baseline tryptase levels should be investigated for presence of mastocytosis. These patients should be considered for life-long venom immunotherapy if evidence for IgE-mediated venom sensitization is found.
- Mast cell activation syndrome is a multisystem disorder with specific diagnostic criteria.
- Documentation of elevated mast cell mediator levels during episodes is critical to diagnosis because some symptoms may not be specific to mast cell activation.

Anaphylaxis is the end result of massive systemic mast cell activation. Physiologic mast cell activation is thought to be beneficial in innate immunity against microorganisms, wound healing, regulation of coagulation, and neutralization of venoms.[1] Pathologic mast cell activation on the other hand is a disproportionate display of mast cell activity often in response to an otherwise harmless trigger. Pathologic mast cell activation may accompany primary disorders of mast cells or may occur in response to a trigger such as an allergen. Sometimes, no recognizable provoking factors for mast cell activation can be elicited.

A specific disorder of mast cells presenting with recurrent episodic mast cell activation has been suggested in the literature for decades; however, diagnostic criteria have been proposed only recently.[2] This disorder, also termed mast cell activation syndrome (MCAS), has many overlapping characteristics with idiopathic anaphylaxis (IA), although MCAS episodes may not always have the full clinical picture of anaphylaxis. This article first discusses the global classification of mast cell disorders, then provides clinical features and diagnostic workup for each category.

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GLOBAL CLASSIFICATION OF MAST CELL DISORDERS

Mast cell disorders can be broadly divided into those involving proliferation and those involving activation, often with a substantial overlap. Most patients with a proliferative mast cell disease such as mastocytosis come to clinical attention because of symptoms caused by mast cell activation.[3] Akin and colleagues[2] recently proposed a global classification scheme for disorders associated with mast cell activation based on whether the mast cells have a primary genetic defect or are simply reacting to an exogenous trigger (**Box 1**).

PRIMARY (CLONAL) MAST CELL DISORDERS

Primary (clonal) mast cell disorder includes mastocytosis and its limited variant monoclonal mast cell activation syndrome (MMAS). These disorders are associated with clonal expansion of mast cells carrying genetic defects in the receptor tyrosine kinase c-kit (most often D816V point mutation). Mastocytosis is characterized by pathologic accumulation of mast cells in various tissues, such as skin and bone marrow, and has a strong proliferative feature in which the proliferative component and mast cell burden in MMAS are more subtle.[4] D816V c-kit mutation is a gain-of-function mutation that has shown to be involved in growth factor independence of hematopoietic cell lines, protection from apoptosis, and enhancement of mast cell chemotaxis.[5] There is a complex interplay between the wild-type and mutated KIT product in the cell. The mutated KIT is primarily located intracellularly, whereas the wild-type KIT is displayed on the cell surface.[6] Wild-type KIT is linked by its ligand stem cell factor, which results in dimerization and autophosphorylation of the receptor. D816V-mutated KIT is constitutively active. Whether this activation is directly involved in reduced mast cell activation threshold is not known. One in vitro model based on

Box 1
Global classification of disorders associated with mast cell activation

- Primary
  - Mastocytosis
  - Monoclonal mast cell activation syndrome
- Secondary
  - IgE-mediated
  - Non–IgE-mediated
    - Physical
    - Associated with inflammatory, infectious, or neoplastic disorders
    - Direct mast cell activation
    - Chronic autoimmune urticaria
- Idiopathic
  - Idiopathic anaphylaxis
  - Idiopathic urticaria and or angioedema
  - Mast cell activation syndrome

Adapted from Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol 2010;126:1099.

overexpression of the mutated KIT in a mast cell line was unable to show enhancement of IgE-mediated mast cell degranulation; however, the extent of this model as an accurate representation of the in vivo environment in mastocytosis is not known.[7]

Mastocytosis can be divided into cutaneous and systemic forms. Cutaneous mastocytosis is the main form of disease in children and is characterized by urticaria pigmentosa or mastocytoma skin lesions without bone marrow or internal organ involvement.[8] There is a rare form of disease involving the whole skin without distinct lesions termed diffuse cutaneous mastocytosis. Cutaneous mastocytosis should be differentiated from urticaria pigmentosa in adults (or mastocytosis in the skin) that often accompanies systemic mastocytosis. Systemic mastocytosis is diagnosed according to the World Health Organization (WHO) criteria, which consist of 1 major and 4 minor criteria.[9] The single major and at least 1 minor, or 3 minor criteria alone, are needed to establish the diagnosis. The major criterion is presence of multifocal compact aggregates of mast cells in tissue biopsies other than skin. The best method to visualize the mast cells is the immunohistochemical stain for tryptase because no other cell stains positively for tryptase (although basophils and myeloid progenitors also contain low levels.) The minor criteria include a serum baseline tryptase level of greater than 20 ng/mL, morphologic abnormalities in mast cells (such as spindle shapes instead of the normal round shape), aberrant CD25 expression by mast cells, and c-kit D816V mutation in peripheral blood or lesional tissue. CD25 expression and c-kit mutation are clonal markers that are not present in clinical samples in which a mild increase in normal mast cell numbers can be seen in reaction to another ongoing inflammatory or neoplastic process (reactive mast cell hyperplasia). Reactive mast cell hyperplasia is thought to reflect a physiologic response of normally produced mast cells to migrate to areas of inflammation such as gut in inflammatory bowel disease, skin in psoriasis, or synovium in rheumatoid arthritis. Mast cells in these conditions may contribute to disease symptoms such as itching or tissue remodeling but do not initiate the pathologic process.

A false-negative result for D816V c-kit mutation is a common clinical problem.[10] This is because the mutation is somatic and is concentrated in tissues with high numbers of pathologic mast cells. Therefore, peripheral blood (and even lesional tissue in cases with low mast cell burden) may not have enough copies of the mutated gene to yield a positive result, especially if a low-sensitive technique such as sequencing is used. A very sensitive method has recently been described that detects an allelic frequency of down to 0.03%; however, the methods to detect the c-kit mutation have not been standardized across laboratories.[11] Aberrant mast cell CD25 expression correlates well with D816V mutation.[12] CD25 can be detected by flow cytometry of the bone marrow aspirate or by immunohistochemistry of the biopsy tissue. Because mast cells are rare events in bone marrow aspirates, at least 500,000 cells should be acquired to be able to analyze the mast cells by flow cytometry. High autofluorescence of atypical mast cells also complicates interpretation of the data. CD25 immunohistochemistry can be performed in routinely processed, paraffin-embedded tissue, including archival specimens, and may be the most easily accessible diagnostic marker in general pathology laboratories.[13] The most common tissue used for the diagnosis of mastocytosis is bone marrow, although some cases were initially diagnosed on gastrointestinal (GI) biopsies. Mast cells in mastocytosis GI biopsies form a typical band in the subepithelial area, generally exceed 100 per high power field,[14] and CD25 staining is positive. Interestingly, tryptase seems to be variably expressed in GI mast cells in mastocytosis and, therefore, CD117 staining should be done in suspected cases.

Monoclonal mast cell activation is a more recently introduced term to designate cases in which patients who, on presentation, have detectable D816V c-kit mutation

or CD25+ mast cells but do not meet the full WHO diagnostic criteria.[15,16] These patients present with symptoms of mast cell activation but lack skin lesions of urticaria pigmentosa. Tryptase levels may be normal or mildly elevated and may not exceed 20 ng/mL at baseline. It is not known if all patients with MMAS will eventually develop systemic mastocytosis or whether some may have a self-limited course with eventual resolution; however, limited data suggest that some patients remain in this state for many years without a cumulative increase in mast cell burden.

ANAPHYLAXIS IN CLONAL MAST CELL DISEASE

It has been clearly established that the incidence of anaphylaxis is increased in mastocytosis. Several reports from Europe and the United States point to an average incidence of 30% lifetime risk of anaphylaxis in patients with mastocytosis.[17–19] Anaphylaxis in mastocytosis and MMAS may be due to an IgE-mediated event, may be caused by direct mast cell activation, or may have no clear triggers. Among IgE-mediated triggers, the risk of hymenoptera anaphylaxis is the best studied. It seems that elevated tryptase levels correlate with the severity of systemic reactions to hymenoptera stings (as well as systemic reactions to venom immunotherapy) regardless of the diagnosis of mastocytosis.[20] One large study from Italy found that approximately 10% of subjects with systemic reactions to hymenoptera had elevated tryptase levels of greater than 11.4 ng/mL.[21] Most of these subjects had mastocytosis or MMAS diagnosed by bone marrow biopsies. In some patients, hymenoptera anaphylaxis may be the only clinical symptom that may lead to the diagnosis of mastocytosis. Most of these patients have evidence of venom-specific IgE on blood or skin tests although specific IgE levels may be lower compared with the nonmastocytosis venom allergic population, possibly due to the adsorption of IgE onto the increased numbers of mast cells, making it less available to be detected in the serum. Venom immunotherapy is indicated indefinitely in this patient population. It is important to establish the diagnosis correctly because fatalities due to insect stings have been reported in patients with mastocytosis.[22,23] IgE-mediated anaphylaxis to drugs and foods are not well studied in mastocytosis. There are occasional case reports of patients with allergy to foods or preservatives.[24] Some patients with mastocytosis have flushing and gastrointestinal symptoms triggered by spicy foods and alcohol; however, these symptoms rarely progress to anaphylaxis. However, cumulative clinical experience suggests that the incidence of IgE-mediated food allergy is not greater in mastocytosis patients compared with the general population. Likewise, it is not known whether the incidence of IgE-mediated drug allergy is increased in mastocytosis.[25] Experience suggests some patients may be at risk for severe non IgE-mediated reactions, such as those experienced with nonsteroidal anti-inflammatory drugs, or with perioperative muscle relaxants. Premedication regimens and a list of perioperative drugs with lower intrinsic mast cell activation properties to be used in anesthesia have been proposed.[26] The incidence of mastocytosis in patients formerly diagnosed with IA is also increased. Akin and colleagues[15] reported that 5 out of 12 patients with IA carried clonal mast cell markers. These findings have been confirmed in larger series from Europe.[27,28]

Symptoms of anaphylaxis experienced in patients with clonal mast cell disease seem to be distinct. It is rare for patients with mastocytosis to experience urticaria or angioedema as the main symptom of mastocytosis, whereas hypotension, syncope, and near syncope are common.[28] This can be a helpful feature in deciding which patients may need further diagnostic workup for mastocytosis. The Spanish Network for Mastocytosis (REMA) reported that male gender, baseline tryptase

greater than 25 ng/mL, absence of urticaria, and presence of hypotension were all associated with a pretest possibility of mastocytosis and have published a score based on these parameters.[28]

Because diagnosis of mastocytosis requires a tissue biopsy, it may be challenging to decide when to aggressively pursue a diagnosis. One study from Holland found that increased levels of the histamine metabolites methylimidazole acetic acid (MIMA) and N-methylhistamine in the urine were a good predictor of mastocytosis when combined with a baseline tryptase level greater than 10 ng/mL.[29] MIMA measurements are not available commercially in the United States but N-methylhistamine is available commercially as a validated mast cell activation marker. Taken together, the author recommends the following evidence-based guidelines in patients presenting with anaphylaxis for referral for a bone marrow biopsy:

1. Adult patients with urticaria pigmentosa
2. Patients with a baseline tryptase of greater than 25 ng/mL if no evidence of urticaria pigmentosa
3. Patients presenting with recurrent hypotensive syncopal or near-syncopal episodes rather than urticaria or angioedema as the main feature of anaphylaxis, regardless of tryptase levels
4. Patients with elevated tryptase (>11.4 ng/mL) and a history of hymenoptera venom anaphylaxis or elevated urinary histamine metabolites
5. Patients with REMA score[28] of less than or equal to 2

MAST CELL ACTIVATION SYNDROME

The presence of a disorder that is distinct from mastocytosis and is characterized by recurrent mast cell activation episodes has been considered for many years and diagnostic criteria have been recently proposed (**Box 2**).[2,30] Because of the nonspecific nature of many symptoms experienced in a mast cell activation episode and the lack of histopathologic findings, it is important to objectively document a marker of mast cell activation during a symptomatic state. The serum marker that is most specific for mast cell activation is tryptase. Tryptase should be measured in serum or plasma within 4 hours of the suspected event. A suggested meaningful increase is $x + 0.2x + 2$ in which x is the baseline tryptase.[30] Thus, a case in which a patient has a baseline tryptase of 5 ng/mL and an increase of greater than 8 ng/mL during a symptomatic period is suggestive of mast cell activation. Also, 24-hour urinary N-methylhistamine, prostaglandin (PG) D2 (PGD2), or 11-bPGF2α levels correlate

Box 2
Proposed diagnostic criteria for mast cell activation syndrome (all 3 must be present)

1. Episodic recurrent symptoms consistent with mast cell activation in more than 1 organ system (skin, GI, cardiovascular, respiratory, nasoocular)
2. Decrease in frequency or severity of symptoms in response to mast cell mediator therapy (H1 and H2 antihistamines, leukotrienes, cromolyn, glucocorticoids)
3. Documentation of increased mast cell activation products above baseline in at least 2 symptomatic episodes (tryptase is the preferred marker; urinary histamine metabolites and PGD2 or 11-b-PGF2α are less specific)

Adapted from Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol 2010;126:1099.

with mast cell activation when the collection period covers or starts immediately after a symptomatic period. However, specific cutoff limits and the specificity of these markers for mast cell activation have not been established. For example, PGD2 may also be produced by activated eosinophils.[31]

Akin and colleagues[2] initially proposed the term MCAS to designate an idiopathic systemic syndrome presenting with multisystem mast cell activation symptoms documented by increased mast cell mediator levels during attacks, which was distinct from clonal and IgE-mediated disorders. Subsequently, experts at an international conference adopted the diagnostic criteria; however, they proposed that the term be used regardless of presence of a clonal or IgE-mediated disorder.[30] Thus, a patient presenting with mast cell activation symptoms would be first evaluated for presence of MCAS criteria, then be classified into primary, secondary, or idiopathic categories, therefore expanding the scope of the syndrome. This is an area that still lacks universal consensus and, in practice, most clinicians would reserve the term for patients in whom no clear cause for episodes is found.

The clinical overlap between MCAS and IA is also significant. Some experts propose replacing the term IA with MCAS because the latter is a more mechanistic and inclusive terminology because, in patients with IA, not all episodes may rise to the severity of anaphylaxis, especially in those who are on maintenance antihistamine or disease-modifying therapy.

Table 1 provides a comparison of the most pertinent clinical features of mastocytosis and idiopathic MCAS.

MANAGEMENT OF RECURRENT ANAPHYLAXIS ASSOCIATED WITH MAST CELL ACTIVATION SYNDROME

In patients with recurrent anaphylaxis associated with MCAS, the most important step is to clarify if the patient has a clonal, an IgE-mediated, or an idiopathic mast cell disorder. Management of IgE-mediated disorders relies heavily on trigger avoidance, availability of multiple doses of self-injected epinephrine, and desensitization in certain circumstances such as with venom anaphylaxis. Patients with clonal and idiopathic MCAS are generally

Table 1
Comparison of clinicopathologic features of mastocytosis and idiopathic mast cell activation syndrome

Clinicopathologic Feature	Mastocytosis	MCAS
Urticaria and angioedema	Rare	Often present
Hypotensive episodes	Common	May be present
Urticaria pigmentosa	Often present	Absent
Serum baseline tryptase	Often >20 ng/mL	Often <20 ng/mL
Tryptase during the event	Elevated	Elevated
CD25+ mast cells	Yes	No
c-kit D816V mutation	Yes	No
Mast cell clustering in tissue biopsies	Yes, particularly around blood vessels	No, or minimal, not exceeding 2–3 cells
Mast cell shape in bone marrow	Spindled	Round and fully granulated
Urinary mast cell mediators	Elevated	Elevated
Response to H1 antihistamines	Yes	Yes

placed on a maintenance H1-antihistamine therapy (once or twice daily long-acting antihistamine). Siebenhaar and colleagues[32] recommend a stepwise approach in which additional drugs, including H2 antihistamines, antileukotrienes, oral cromolyn, and steroids, are added in unresponsive patients. It is the author's experience that patients with idiopathic MCAS respond similarly to treatment options suggested for IA, including ketotifen,[33] whereas this drug is generally not superior to conventional antihistamines in patients with clonal mast cell disease.[34] Aspirin therapy has been reported beneficial in patients with MCAS who have elevated urinary PG levels.[35] Omalizumab has shown beneficial in suppressing mast cell activation episodes in all clinical subtypes of MCAS, although exact mechanism of action is unknown.[36–38] Patients with clonal mast cell disease who are not responsive to the symptomatic management and who continue to have life-threatening symptoms may be candidates for mast cell cytoreductive therapy, such as interferon-alpha, cladribine, or tyrosine kinase inhibitors.[39] Mast cell clonality should be clearly established before considering cytoreductive therapy and the risks and the benefits of the particular drugs should be carefully discussed with the patient, including the possible investigational nature of the proposed therapy.

FUTURE DIRECTIONS

Despite increased awareness and recognition of MCAS in the last decade, much remains to be elucidated regarding its pathogenesis, disease markers, and treatment. Prospective multicenter trials are needed to validate the proposed diagnostic criteria and identify patient subgroups that may respond differently to therapy. The incidence and subtypes of MCAS in the pediatric population have not been systematically investigated. Although tryptase is the most specific marker for mast cell activation, it has to be checked within a few hours after the episode and may not be elevated in all patients with anaphylaxis. The specificity of urinary PGF2 is not known. Therefore, identification of additional markers of mast cell activation and anaphylaxis would facilitate the diagnosis of MCAS. Finally, development of new drugs targeting intracellular mast cell activation mechanisms and mediators, as well as mast cell survival, is needed. All of these efforts should benefit from basic mechanistic human mast cell research, although they are hampered to a certain degree by the difficulty in obtaining ex vivo human mast cells and the time and cost involved in generating human mast cell cultures. A variety of human mast cell lines, including HMC-1,[40] LAD2,[41] and ROSA,[7] each with its own advantages and shortfalls have been established that could complement these efforts.

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