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Mast Cell Activation Syndrome: A Review

Marianne Frieri · Reenal Patel · Jocelyn Celestin

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Abstract Mast cell activation syndrome (MCAS) is a condition with signs and symptoms involving the skin, gastrointestinal, cardiovascular, respiratory, and neurologic systems. It can be classified into primary, secondary, and idiopathic. Earlier proposed criteria for the diagnosis of MCAS included episodic symptoms consistent with mast cell mediator release affecting two or more organ systems with urticaria, angioedema, flushing, nausea, vomiting, diarrhea, abdominal cramping, hypotensive syncope or near syncope, tachycardia, wheezing, conjunctival injection, pruritus, and nasal stuffiness. Other criteria included a decrease in the frequency, severity, or resolution of symptoms with anti-mediator therapy including H_1 and H_2histamine receptor antagonists, anti-leukotrienes, or mast cell stabilizers. Laboratory data that support the diagnosis include an increase of a validated urinary or serum marker of mast cell activation (MCA), namely the documentation of an increase of the marker above the patient's baseline value during symptomatic periods on more than two occasions, or baseline serum tryptase levels that are persistently above 15 ng/ml, or documentation of an increase of the tryptase level above baseline value on one occasion. Less specific assays are 24-h urine histamine metabolites, PGD_2 (Prostaglandin D_2) or its metabolite, 11-β-prostaglandin F_2 alpha. A recent global definition, criteria, and classification include typical clinical symptoms, a substantial transient increase in serum total tryptase level or an increase in other mast cell derived mediators, such as histamine or PGD2 or their urinary metabolites, and a response of clinical symptoms to agents that attenuate the production or activities of mast cell mediators.

Keywords Mast cell activation · Mast cell activation syndrome · Mastocytosis · Idiopathic anaphylaxis · Clonal MCAD · Nonclonal MCAD · Classification · Treatment

M. Frieri (✉)
Department of Medicine and Pediatrics, Nassau University Medical Center,
2201 Hempstead Turnpike,
East Meadow, NY 11554, USA
e-mail: mfrieri@numc.edu

R. Patel
Division of Allergy Immunology, Department of Medicine,
Nassau University Medical Center, 2201 Hempstead Turnpike,
East Meadow, NY 11554, USA
e-mail: reenalrpatel@gmail.com

J. Celestin
Division of Allergy and Immunology, Albany Medical College,
176 Washington Avenue Extension, Suite 102,
Albany, NY 12203-5304, USA
e-mail: celestj@mail.amc.edu

Introduction

Classic mast cell activation occurs through FcεRI, a tetrameric complex of an extracellular α chain that binds the Fc portion of IgE, a transmembrane β chain, and 2 disulfide-linked transmembrane γ chains that participate in signal transduction [1].When adjacent receptors are crosslinked by multivalent antigens or haptens, the phosphorylation of the β and γ chains within the immunoregulatory tyrosine-activation motifs (ITAMs), common to other transmembrane receptors, recruits and activates the nonreceptor tyrosine kinases Lyn and Syk and leads to several pathways of signal transduction [2]. Syk activates the phosphatidylinositol-specific phospholipase (PL) Cγ1 with generation of the intracellular second messengers inositol-1,4,5-trisphosphate

(IP3) and diacylglycerol from inositol-4,5-bisphosphate [3]. Stem cell factor (SCF), in addition to its role in mast cell development, is a potent mast cell agonist acting through the transmembrane tyrosine kinase receptor c-*kit* [4]. SCF is the product of fibroblasts and stromal cells but has also been localized to alveolar macrophages and endothelial cells [5–7]. SCF in humans causes immediate mast cell degranulation and generation of PGD2 and leukotriene C4 [8]. It is a chemotactic factor for human mast cells and prevents their apoptosis [9], and the c-kit receptor ligand can function as a mast cell chemoattractant [10].

Ito demonstrated that stem cell factor programs the mast cell activation phenotype and that a major role in the homeostatic control of mast cell activation. This observation has potential relevance to mast cell-driven disease and the development of novel approaches for the treatment of allergic disorders [11]. Gilfillan reviewed the tyrosine kinase regulation of mast cell activation and the role of KIT [12]. KIT (CD117) is a protein of approximately 145 kDa whose expression is largely but not exclusively restricted to cells of hematopoietic lineage and melanocytes. Mast cell mediator release represents a pivotal event in the initiation of inflammatory reactions associated with allergic disorders. These responses follow antigen-mediated aggregation of immunoglobulin E (IgE)-occupied high-affinity receptors for IgE (Fc epsilon RI) on the mast cell surface, a response which can be further enhanced following stem cell factor-induced ligation of the mast cell growth factor receptor KIT (CD117) [12].

The switch pocket (SP) of KIT regulates its catalytic conformation. Bai identified two SP inhibitors, DP-2976 and DP-4851, and examined them for effects on neoplastic mast cell proliferation and activation. Overall, SP inhibitors represent an innovative mechanism of KIT inhibition whose dual suppression of KIT D816V neoplastic mast cell proliferation and SCF-enhanced mast cell activation may provide significant therapeutic benefits [13]. Bax reviewed the cytokinergic IgE action in mast cell activation [14]. These authors have attempted to alert the reader to the different roles of IgE in the activation of mast cells and basophils, inhibitors of oxidative stress, and (Histamine Receptor Factor) binding to IgE. Cytokinergic activity is no mere academic curiosity, relevant only to model hapten-specific mouse antibodies acting on cultured mast cells, but it is likely also to be relevant in humans. Most provocative perhaps may be the conjecture that these cytokinergic IgEs play a part in triggering and perpetuating the symptoms of allergic rhinitis and asthma [14]. The conjectural mechanisms they have outlined of the events that follow the binding of a cytokinergic IgE to the mast cell need to be tested. Detailed structural and dynamic studies have so far been confined to a single case (SPE-7 IgE), and need to be extended to other cytokinergic IgEs to establish the generality of the conclusion [14].

Mast Cell Activation Criteria

Akin reviewed mast cell activation syndrome and proposed diagnostic criteria (Table 1) [15••]. The term mast cell activation syndrome (MCAS) is finding increasing use as a diagnosis for signs and symptoms involving the dermis, gastrointestinal tract, and cardiovascular system, frequently accompanied by neurologic complaints. Postural tachycardia syndrome(POTS) is a disabling condition in MCAS that commonly affects otherwise normal young females that can present with a flushing disorder, shortness of breath, headache, lightheadedness, excessive diuresis, and gastrointestinal symptoms such as diarrhea, nausea, and vomiting [16]. They can have hyperadrenergic postural tachycardia and are diagnosed by episodes of flushing and abnormal increases in urine methylhistamine. Beta-blockers should be used with great caution in those patients, and treatment directed against mast cell mediators may be required [16].

Mast Cell Activation Classification

The classification of diseases associated with MCAS can be primary with hypotension associated with a clonal proliferative mast cell disorder (mastocytosis). Secondary MCA may be due to allergic disorders, physical urticarias, chronic autoimmune urticaria, and idiopathic anaphylaxis. Angioedema and urticaria can also at times be associated with chronic inflammatory or neoplastic disorders. In secondary MCA, symptoms can be infrequent to frequent, and resultant disease can be sporadic or chronic. Cases of idiopathic MCA may occur in which there is no identifiable cause. However, the search must continue for the cause of these idiopathic disorders, including the possibility that mast cell activation might be related to a yet-to-be-identified endogenous or environmental stimulus, intrinsic mast cell defect, or both, resulting in a hyperactive mast cell phenotype [15••]. Some idiopathic events can follow basophil activation rather than MCA or result from activation of both mast cells and basophils. Selective activation of basophils can be explained by the differential expression of critical cell surface receptors on basophils and mast cells, and some triggers of mediator release might preferentially activate basophils [15••]. Patients have often undergone multiple extensive medical evaluations by different physicians in varied disciplines without a definitive medical diagnosis until a diagnosis of MCAS is made. MCAS as a distinct clinical entity has not been generally accepted and there are no definitive criteria for diagnosis. Based on our

Table 1 Proposed criteria for mast cell activation syndrome[a] (From Akin et al. [15••]; reproduced with permission from Mosby)

1. Episodic symptoms consistent with mast cell mediator release affecting ≥2 organ systems evidenced as follows:
   a. Skin: urticaria, angioedema, flushing
   b. Gastrointestinal: nausea, vomiting, diarrhea, abdominal cramping
   c. Cardiovascular: hypotensive syncope or near syncope, tachycardia
   d. Respiratory: wheezing
   e. Naso-ocular: conjunctival injection, pruritus, nasal stuffiness
2. A decrease in the frequency or severity or resolution of symptoms with antimediator therapy: H_1- and H_2-histamine receptor inverse agonists, antileukotriene medications (cysteinyl leukotriene receptor blockers or 5-lipoxygenase inhibitor), or mast cell stabilizers (cromolyn sodium).
3. Evidence of an increase in a validated urinary or serum marker of mast cell activation: documentation of an increase of the marker to greater than the patient's baseline value during a symptomatic period of ≥2 occasions or, if baseline tryptase levels are persistently >15 ng, documentation of an increase in the tryptase level above baseline value on 1 occasion. Total serum tryptase level is recommended as the mark of choice; less specific (also from basophils) are 24-h urinary histamine metabolites of PGD_2 or its metabolite 11-β-prostaglandin F_2.
4. Rule out primary and secondary causes of mast cell activation and well defined clinical idiopathic entities.

From Akin et al. [15••]; reproduced with permission from Mosby

PGD2 Prostaglandin D2

[a] MCAS for now remains an idiopathic disorder; however, in some cases, it could be an early reflection of a monoclonal population of mast cells, in which case with time it could meet the criteria for MMAS as 1 or 2 minor criteria for mastocytosis are fulfilled

current understanding of MCA and resulting pathology, this article explores and proposes criteria for the diagnosis MCAS and discusses that syndrome within the context of other disorders involving mast cells as a basis for further scientific study and validation.

Activation of tissue mast cells and abnormal growth and accumulation in various organs are typically found in primary mast cell disorders such as mastocytosis [17]. Patients with clonal mast cell disease such as systemic mastocytosis, often present with signs and symptoms that are characteristic of MC mediator release [18].

Idiopathic Anaphylaxis and Mastocytosis

There are differences in the clinical presentation of anaphylaxis in patients with indolent systemic mastocytosis versus idiopathic anaphylaxis [18]. Patients with indolent systemic mastocytosis usually do not present with urticaria during anaphylactic episodes. Generally, serum tryptase levels are significantly elevated with indolent systemic mastocytosis in contrast to idiopathic anaphylaxis, where there is a higher frequency of urticaria and significantly higher levels of serum IgE [18].

Since the symptoms of idiopathic anaphylaxis may be identical to those of anaphylactic episodes of known causes, patients should undergo an intensive evaluation, including a meticulous history and specific laboratory studies to exclude systemic disorders, such as systemic mastocytosis. The laboratory evaluation may include a serum tryptase level when the patient is asymptomatic, a ratio of β-tryptase to total tryptase during an event, and selective allergy skin testing [19]. Although uncommon in children, idiopathic anaphylaxis is a diagnosis of exclusion common in adults who are referred to allergists for evaluation of anaphylaxis with negative skin tests, negative allergic dietary history, and no associated diseases such as mastocytosis. Preventive medications consist of oral corticosteroids, H_1- and H_2-antihistamines, including Ketotifen, and anti-leukotrienes. Fatalities are rare and the prognosis may gradually improve over time. Recurrent idiopathic anaphylaxis presents with allergic signs and symptoms of hives and angioedema which is a distinguishing feature. The clinician should rule out an identifiable allergic etiology, consider mastocytosis and carcinoid syndrome, and treat with H_1- and H_2-antihistamines, epinephrine, and steroids [20, 21•]. Mast cell membrane stabilizers and antihistamines do not appear to affect urine histamine levels [22]. A limitation of the PGD_2 assay is that patients ideally should be off aspirin and nonsteroidal anti-inflammatory drugs during the 24-h urine collection and symptomatic at the time of the test. Recurrent idiopathic anaphylaxis should not be confused with benign cutaneous flushing where recurrent flushing of the "blush area" is precipitated by emotion, exercise, temperature change, and spicy foods. Women are noted to be at greater risk than men and may experience feeling of increased body heat, cognitive dysfunction, and abdominal complaints which do not respond to medications [23].

Clonal and Non-Clonal MCAD

Alvarez-Twose reviewed MCAD in 83 patients [24]. Patients were divided into two main groups: c-MCAD

(clonal mast cell activation disease) and nc-MCAD (non-clonal mast cell activation disease). The majority of patients in the c-MCAD met the WHO criteria for mastocytosis and were either classified as indolent systemic mastocytosis without skin lesions [ISM (−)] or others. In contrast to nc-MCAD, all c-MCAD patients expressed CD25, kit mutation or were positive for the human androgen receptor assay. c-MCAD was most common in men and they displayed a higher frequency of pre-syncopal and syncopal episodes in the absence of urticaria or angioedema. Also, they had a higher incidence of cardiovascular problems and insect-related episodes associated with higher baseline levels of serum tryptase. So, patients with clonal MCAD and indolent systemic mastocytosis without skin lesions, displayed unique clinical and laboratory features different from non-clonal MCAD patients. Thus, a significant percentage of clonal MCAD patients were considered as true ISMs(−) diagnosed during early phases of the disease [24]. An increasing numbers of patients are now being informed that their clinical findings are due to MCA that is neither associated with mastocytosis nor with a defined allergic or inflammatory reaction.

MCAD includes mast cell activation syndrome (MCAS), mast cell leukemia (MCL), systemic mastocytosis (SM) as defined by the WHO criteria, indolent systemic mastocytosis, smoldering systemic mastocytosis, aggressive systemic mastocytosis, and systemic mastocytosis with an associated clonal hematologic and non-mast cell lineage disease [25]

Hamilton prospectively reviewed a group of patients with MCAS [26]. Their symptoms include flushing and other cutaneous manifestations, and neuropsychiatric symptoms such as headache, poor concentration, and memory loss. Eighteen patients were evaluated from 2006 to 2009 and had at least 4 of the signs and symptoms of abdominal pain, diarrhea, flushing, dermatographism, memory and concentration difficulties, or headache. Response to treatment with anti-MC mediator medications was assessed based on established criteria. Laboratory tests indicating MC mediator release and histopathology and immunohistochemical studies on gastrointestinal biopsy samples were performed, revealing that 94 % patients had abdominal pain, 89 % had dermatographism, 89 % had flushing, and 72 % had the constellation of all 3 symptoms. Patients additionally had headache, diarrhea, and memory and concentration difficulties [26].

In patients with MCA, mast cells appear to be clonal cells, but criteria for diagnosing mastocytosis are not met. A working conference was organized in 2010 to define criteria for diagnosing MCA and related disorders, and to propose a global unifying classification of all MC disorders and pathologic MC reactions [27••]. This classification includes three types of 'MCA syndromes' (MCASs), namely primary, secondary and idiopathic (Table 2). MCA is now defined by robust and generally applicable criteria, including (1) typical clinical symptoms, (2) a substantial transient increase in serum total tryptase level or an increase in other MC-derived mediators, such as histamine or PGD2 or their urinary metabolites, and (3) a response of clinical symptoms to agents that attenuate the production or activities of MC mediators. These criteria should assist in the identification and diagnosis of MCAS patients, and in avoiding misdiagnoses or over interpretation of clinical symptoms in daily practice. They should stimulate research in order to identify and exploit new molecular mechanisms and therapeutic targets [27••]. All patients had at least one positive laboratory test result for an increased MC mediator level. Of the response to treatment criteria, 67 % of the patients had either a complete or major regression in symptoms while taking medications targeting MC mediators.

There was no significant difference in the numbers of intestinal mucosal MCs between the patients and healthy control subjects. MCAD might be the underlying cause of unexplained symptoms when several organ systems are involved, such as the gastrointestinal tract and the skin. It is especially important to be able to recognize the constellation of clinical features because response to anti-MC mediator medications is often excellent.

Several Therapeutic Agents

Pardanani recently updated the criteria for systemic mastocytosis in adults, performed risk stratification,

Table 2 Classification of diseases associated with mast cell activation disorder (*From* Akin et al. [15••]; reproduced with permission from Mosby, Inc.)

1. Primary
a. Hypotension with an associated clonal proliferative mast cell disorder (mastocytosis)
b. MMAS*
2. Secondary
a. Allergic disorders
b. Mast cell activation associated with chronic inflammatory or neoplastic disorders
c. Physical urticarias
d. Chronic autoimmune urticaria
3. Idiopathic
a. Anaphylaxis
b. Angioedema
c. Urticaria
d. MCAS

and discussed their current treatment. He concluded that a good first step in establishing the prognosis for patients with systemic mastocytosis is to classify them into four sub-groups: indolent (SM), aggressive (ASM), non-mast cell lineage disease (SM-AHNMD), and mast cell leukemia (MCL). While indolent SM patients have a normal life expectancy requiring only symptomatic treatment, ASM patients with disease-related organ dysfunction often require interferon-α with or without oral corticosteroids. In that setting, Cladribine has broad therapeutic activity, especially when rapid debulking of the tumor is warranted. Similarly, Imatinib has a therapeutic role in Imatinib-sensitive Kit mutation and KITD816-unmutated patients. In patients with SM-AHNMD, Hydroxyurea has modest utility. Finally, MCL patients have a dismal prognosis with only a 2-month median survival rate [28]. We earlier reported a case of lymphadenopathic mastocytosis in a patient who presented with SM with eosinophilia and biclonal gammopathy who eventually died of mast cell leukemia [29]. Gotlib noted that eosinophils and mast cells serve critical roles as part of the host immune response and in maintenance of normal homeostasis. These cell types can undergo neoplastic transformation due to the development of clonal molecular abnormalities that arise in early hematopoietic progenitors [30].

Treatment

Since there is no cure for MCAD, an individual's treatment plans should target specific symptoms. The primary treatment is aimed at avoidance of triggers that have been identified by the physician and the patient (Tables 3 and 4). Primary therapy for MCAD involves the use of H_1 - and H_2-histamine receptor antagonists, antileukotriene medications, or mast cell stabilizers. Newer therapies are being identified, but still require further investigations. These therapies include humanized murine monoclonal antibody omalizumab and tyrosine kinase inhibitors [31]. If anaphylactoid or anaphylaxis is of concern, these patients should undergo appropriate prophylactic treatment and education on the use of epinephrine.

Conclusions

Mast cell activation syndrome is a very complicated disorder that can present with common and unusual symptoms in multiple organ systems. Hence, it is imperative that any physician who suspects that his or her patient's symptoms fit the diagnosis of mast cell activation syndrome should consider the proposed criteria for diagnosis. Patients suffering with MCAD need assistance in identifying their triggers and education on proper avoidance. Therapy will primarily consist of avoidance of these triggers and mast cell stabilizing agents.

Table 3 Selected mast cell activators of clinical relevance

1. IgE dependent
 a. Allergen
 b. Anti-IgE IgG
2. IgE independent
 a. IgG through FceRI
 b. Anti-FceRI IgG
 c. Bacterial components
  I. Peptidoglycan: TLR2/6
  II. LPS: TLR4
  III. fMLP
 d. C3a, C5a
 e. Cytokines/chemokines
 f. SCF, NGF, MIP-1a
 g. Neuropeptides
 h. Drugs
  I. Opioids
  II. Muscle relaxants,
  III. Radiocontrast material
  IV. Adenosine
 i. Physical stimuli
  I. Heat, cold, pressure
 j. Hormones
  I. Estrogen, progesterone, a-MSH, CRH

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a-MSH a-Melanocyte–stimulating hormone; *CRH* corticotropin-releasing hormone; *fMLP* formyl-methionyl-leucyl-phenylalanine; *MIP-1a* macrophage inflammatory protein 1a; *NGF* nerve growth factor; *TLR* Toll-like receptors

Table 4 Disease states associated with evidence of mast cell activation

Disease	Potential mechanisms
1. Atopic disease	Allergen-specific IgE
2. Chronic autoimmune urticaria	Anti-IgE or anti-FceRI autoantibodies
3. Autoimmunity	IgG receptor, complement
4. Chronic infections	TLRs, IgG, complement
5. Drug allergy	Specific receptors, complement, IgE
6. Physical stimuli	Direct mast cell activation
7. Neoplasms	Complement, cytokines

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- •• Of major importance

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