Mini Review
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The mast cell activation syndrome: a mini review

Abstract

For decades the only recognized disease states associated with mast cells were urticaria pigmentosa and systemic mastocytosis. Since about 1991, publications regarding variations of disease states associated with mast cells have appeared in the medical literature. These disorders present with signs and symptoms involving the dermis, gastrointestinal tract, cardiovascular system and sometimes neurological complaints. The spectrum of mast cell diseases has thus expanded from what was a limited but well defined disease state (systemic mastocytosis) to subtler presentations, such as the mast cell activation syndrome (MCAS). This review will present a brief history of the mast cell and its subsequent association with multiple clinical disease states, as well as the criteria needed to delineate and classify these disease states into categories.

Keywords: mast cell, mast cell activation syndrome, systemic mastocytosis, monoclonal, clonal, histamine, mast cell mediators

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Abbreviations: MCAS, mast cell activation syndrome; SM, systemic mastocytosis; MC, mast cell; MMCAS, monoclonal mast cell activation syndrome; MCAD, mast cell activation disease

Introduction

The mast cell was first identified in frogs by German pathologist Friedrich von Recklinghausen[1] Mast cells in humans were first identified in 1877 in connective tissues. Identified by Paul Ehrlich, he termed these cells "mastzellan" or "well nourished" cells due to their rich cellular content.[2] In 1887 German dermatologist Unna PG associated mast cells with human disease by defining the rare skin disease: urticaria pigmentosa.[3] By 1949 mast cells were linked to internal disease in what today is known as systemic mastocytosis.[4] The first mast cell mediator was identified in 1937 when heparin was found to be present in mast cell granules.[5,6] Histamine was identified in mast cells in 1953.[7,8] Over the ensuing decades the hematopoietic origin of the mast cell was discovered, as well as dozens of molecular signals originating from the mast cells (MC mediators).

Mast cells are capable of responding to allergen specific as well as nonspecific triggers. Allergen specific responses are conferred by surface bound specific IgE molecules in atopic individuals. 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. Mast cells are located in tissues which interface with the external environment, e.g. the skin and mucosa, the GI tract, the respiratory system and ocular conjunctivae in proximity to blood vessels and nerves. Mast cells are also interstitially distributed in bone marrow, liver, spleen and lymph nodes. The tissue distribution of mast cells and their activation by multiple signals can cause either sporadic or chronic symptoms. These symptoms range from localized itching or nasal congestion to abdominal cramping to systemic symptoms such as anaphylaxis.[9]

In 1991 John Oates & Jack Roberts of Vanderbilt University hypothesized the existence of a spectrum of disorders of mast cell mediator release, e.g. mast cell activation with little to no MC proliferation unlike cutaneous or systemic MC diseases which are thought to be a disorder of MC proliferation.[10] In 2007 a "monoclonal MC activation syndrome" (MMCAS) was described along with diagnostic criteria to define this syndrome.[11] In 2008 a new conceptualization (Table 1) was introduced by MC researchers, Akin C et al.,[12] who proposed that all MC disease is a manifestation of aberrant MC activation and should be designated as "mast cell activation disease" (MCAD) which described a full range of pathologic MC states. This included both proliferative MCAD and relatively non-proliferative MCAS (mast cell activation syndrome) diseases. Examples of the former would be urticaria pigmentosa, systemic mastocytosis, and MMCAS (monoclonal MC activation syndrome). Akin et al. further divided these syndromes into 3 categories: primary, secondary, and idiopathic mast cell activation[13] (Table 2). Symptomatically, systemic mastocytosis is characterized by hypotension with an associated clonal proliferative mast cell disorder and an increase in mast cells in tissues such as skin, bone marrow, and other internal organs. The symptoms may be similar in MMCAS but these patients lack characteristic bone marrow mast cell clusters identified in mastocytosis (>15 mast cells per high power field) and have normal or only slightly increased serum tryptase levels. In MMCAS the number of bone marrow mast cells would be <15 mast cells/hpf and the mast cells would be found to be hypo granulated and spindle shaped.

Both SM and MMCAS are considered to be classified as primary mast cell disorders. The primary or clonal disorders are those in which there is an inherent genetic defect in the mast cells or their progenitors (e.g. the D816V c-kit mutation, a single base pair substitution from aspartic acid (D: wild type) to valine (V: mutant) in tyrosine kinase at codon 816 in mast cells and their progenitors), presumably reducing their activation threshold. Less well known than systemic mastocytosis is MMCAS, It is part of the clonal classification in which mast cells exhibit aberrant genetic and surface markers. Baseline tryptase levels are often normal in these patients but can increase during symptomatic episodes. MMCAS does not fit the WHO criteria for Systemic Mastocytosis[14] (Table 2). One or two minor criteria may be present (e.g. c-kit mutation or CD25 expression on bone marrow analysis). The characteristic clinical presentation of these patients includes episodic symptoms of mast cell degranulation, such as flushing, lightheadedness, abdominal cramping, nausea, and diarrhea. The non-clonal disorders (secondary and idiopathic) include a broader range of more common diagnoses, which can be secondary to allergic disease, physical or chronic urticaria, chronic inflammation, neo plastic processes, and the idiopathic mast cell activation syndrome (MCAS) as well as all cases of idiopathic anaphylaxis. There are many descriptions of secondary mast cell activation disease states. Less well known is idiopathic MCAS. It is a disorder in which no

clonal markers (e.g. c-kit D816BV mutation or CD25 expression on mast cells) have occurred. In 2012 Valent p & Akin C et al. proposed international consensus criteria for the diagnosis of the mast cell activation syndrome:[14]

1) Recurrent or chronic symptoms of mast cell activation

2) Laboratory results showing evidence of mast cell activation (e.g. serum tryptase or urinary N-methyl histamine, prostaglandin D2 PGD2 and prostaglandin F2-alpha PGF2-alpha

3) Response of clinical symptoms to anti mediator therapy (Table 3). The symptoms of idiopathic MCAS are much the same as those described for MMCAS noted above.

Table 1 Classification of diseases associated with mast cell activation

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

*Monoclonal Mast Cell Activation Syndrome; **Mast Cell Activation Syndrome

By the time a patient presents to be considered as having the MCAS, he or she has already undergone a work-up to rule out other diseases such as the carcinoid syndrome and other malignant conditions, e.g. pheochromocytoma and medullary thyroid cancer, estrogen or testosterone deficiency, inflammatory bowel disease, autoimmune disease, reactions to environmental toxins, and allergic reactions. A crucial consideration in the diagnostic work-up is to decide when a bone marrow biopsy should be done. A baseline tryptase level of >20ng/ml or those who have syncopal/ hypotensive episodes (regardless of tryptase levels) should have bone marrow biopsies. If a patient presents with urticaria or angioedema, bone marrow biopsy probably would not be a consideration (urticaria and angioedema are rarely seen during mast cell activation syndromes in mastocytosis.[15]

A unique situation occurs in patients who have had systemic reactions to Hymenoptera. They may have a primary or clonal mast cell disease and a co-existing IgE mediated allergy. In these patients insect sting reactions can be extremely severe. Patient with idiopathic mastocytosis and Hymenoptera allergy are recommended to have venom immunotherapy indefinitely because systemic reactions have been reported after stopping VIT[16] Elevated tryptase levels signal a higher risk for serious Hymenoptera reactions whether or not mastocytosis is present. It has been determined that in patients with venom anaphylaxis, a tryptase level of less than 11.4ng/ml helps to differentiate non clonal from clonal disease for most patients. In one study[17] 13.8% of patients with anaphylaxis to Hymenoptera were found to have underlying clonal mast cell disorders. 29 of 31 patients with an elevated tryptase level (>11.4ng/ml) and a history of anaphylaxis to Hymenoptera stings showed a clonal abnormality consistent with either an indolent SM or MMAS.

**Histamine blockers HR1 +/-HR2 inverse agonists

To summarize laboratory findings, patients with systemic mastocytosis usually have elevated baseline levels of tryptase (>20ng/ml). This is in contrast to patients with MMCAS and MCAS who usually present with normal or slightly elevated baseline tryptase levels less than 20 ng/ml. Elevations in tryptase levels during symptomatic episodes are possible and are confirmatory of mast cell activation. Tryptase levels should be measured within 4hours of the symptomatic episode. A significant elevation of tryptase would be a level of 20% above baseline plus 2ng/ml. The serum and urinary arachidonic acid metabolites PGD2 and PGF2-alpha are usually elevated. The normal ranges for the serum metabolites at the Inter science Institute Laboratory are: SERUM: PGD2 (35-115pg/ml serum) and PGF2-alpha (80-240pg/ml serum); URINE: PGD2 (100-280 ng/24hr) and PGF2-alpha (375-800ng/24hr urine). The urine measurements are done on a 24hour specimen.[18]

Table 2 Who 2008 Diagnostic Criteria for Systemic Mastocytosis

	Major Criteria
	Multifocal, dense aggregates of MCs (15 or more) in sections of bone marrow or other extra cutaneous tissues and confirmed by tryptase immune histo chemistry or other special stains.
	Minor Criteria
1.	Atypical or spindled appearance of at least 25% of the MCs in the diagnostic biopsy.
2.	Expression of CD2 and/or CD25 by MCs in marrow, blood, or extra cutaneous organs
3.	KIT codon 816 mutation in marrow, blood, or extra cutaneous organs.
4.	Persistent elevation of serum total tryptase>20 ng/ml.
	Diagnosis of SM made by either (1) major criterion + any one or more minor criteria, or (2) any three minor criteria

Table 3 Criteria for the diagnosis of MCAS

Typical clinical symptoms*
Increase in serum total tryptase by at least 20% above baseline Plus 2 ng/ml during or within 4 hours after a symptomatic period
Response of clinical symptoms to histamine receptor blockers** or 'MC-targeting' agents e.g. Cromolyn
*Symptoms: Flushing, pruritus, urticaria, angioedema, nasal congestion, nasal pruritus, wheezing, throat swelling, headache, hypotension, diarrhea.

Treatment of the symptoms of the mast cell activation syndrome includes medications that target the effects of mast cell mediators and those that stabilize mast cell membranes. Initially treatment includes the second generation of non-sedating H1 anti-histamines (cetirizine, fexofenadine, loratadine) which may be given BID as prophylactic therapy. Doses to 4times what is considered normal may be needed if urticaria is present. For breakthrough symptoms first-generation (sedating) antihistamines may be added, e.g. diphenhydramine or hydroxyzine. H2 antihistamines can be prescribed to treat abdominal symptoms, if present, e.g. ranitidine and famotidine, in BID doses. Mast cell stabilizers such as Ketotifen 1 to 2mg q 12h or Cromolyn sodium in doses of 800 mg/day divided into 4 doses may be helpful for gastrointestinal symptoms. If prostaglandins (PGD2 and PGF2-alpha) are elevated, montelukast 10 mg or aspirin 81 mg/d may provide symptomatic relief. Aspirin can be titrated up to 325mg BID. This would be contra-indicated in patients who have an allergy or intolerance to NSAIDS. Patients who have had anaphylaxis or who have clonal disease with no history of anaphylaxis should be given self-injectable Epinephrine (multiple doses). Some recommend consideration of systemic glucocorticoids as a next step. Although

unproven as yet by clinical studies, second line agents helpful in other disorders of mast cell activation, e.g. drugs effective in chronic spontaneous urticaria: hydroxyl chloroquine, dapsone, cyclosporine or omalizumab) may provide symptomatic relief.[19,20]

Summary

From the initial identification of mast cells in human tissues, diseases caused by aberrant mast cell activation have expanded from the obvious (but rare) symptoms of systemic mastocytosis to a spectrum of disease with subtler presentations, such as the mast cell activation syndrome. This review has presented a historical perspective of the evolution of the identification of these mast cell diseases and the criteria which identify how to categorize a patient's symptoms and laboratory findings. There is a more extensive study of less relevant laboratory studies elsewhere.[21] A synopsis of current treatments is presented.

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Conflicts of interest

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