

Mast Cell Activation Syndromes

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Abbreviations CM Cutaneous mastocytosis · EDS Ehlers-Danlos syndrome · HV Hymenoptera venom · IMCAS Idiopathic mast cell activation syndrome · MC Mast cell · MCA Mast cell activation · MCAS Mast cell activation syndromes · SM Systemic mastocytosis · VIT Venom immunotherapy

Opinion statement

Mast cell activation syndromes (MCAS) are disorders associated with mast cell activation (MCA), and include Primary MCAS, Secondary MCAS and Idiopathic MCAS. MCAS are characterized by clinical symptoms of MCA in cutaneous, gastrointestinal, respiratory, cardiovascular, musculoskeletal and neurological organs. Mast cell (MC) mediators such as tryptase in serum, and/or histamine or prostaglandin urinary metabolites are typically elevated at base line or transiently during episodes of MCA, and there is a total or partial response to mast cell mediators controller medications. In primary MCAS an activating point mutation at codon 816 of *KIT* on MC is present in most cases of Systemic Mastocytosis (SM) and Monoclonal Mast Cell Activation Syndrome (MMCAS) and is absent in secondary and Idiopathic MCAS. MCAS 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. This update on mast cell disorders (MCD) provides an insight into the classification, clinical presentations, diagnosis, treatment and management. We describe associated conditions, such as Hymenoptera Reactions, Familial Tryptasemia, Postural Orthostatic Tachycardia Syndrome and Ehlers-Danlos Syndrome.

Introduction

MC are hematopoietically derived immune cells, which are generated in the bone marrow, travel in immature form in the peripheral blood and home in most tissues. It carries out physiologic roles in innate host defense against infectious pathogens, neutralization of toxins, and both positive and negative regulation of the adaptive immune response [1, 2].

MC have pathologic roles in MCAS, immediate hypersensitivity reactions and anaphylaxis [1, 3, 4].

There is enough evidence that MC play a role in inflammatory, infectious, and functional disorders of the lungs, eyes, skin, joints, and gastrointestinal tract [5•]. In gastroenterology, for instance, the role of MC has been studied in irritable bowel syndrome, inflammatory bowel disease, and infectious disorders of the gastrointestinal tract [6–14].

MC in skin, mucosa and connective tissue location contain pro inflammatory mediators and express many surface membrane receptors including the high-affinity IgE receptor Fc RI [1, 2, 15]. These receptors can aggregate with different ligands including allergens bound to IgE and activate signal transduction leading to calcium influx and the release of inflammatory mediators, which bind to receptors in multi organ systems leading to the symptoms of anaphylaxis [16••] (Fig. 1a). Following activation, MC release the contents of their granules: Histamine, tryptase, chymase, proteoglycans (heparin), platelet-activating factor, prostaglandin D2, leukotriene

(C4, D4, and E4) cytokines (IL-1,3,4,5,6,8,10,13,16 and TNF- α), chemokines and renin. The clinical features of each mediator is listed in Table 1 [16••, 17–20].

Mast Cell T type (MC_T) and mast cell TC type (MC_{TC}) are types of human MC. MC_T are normally the predominant type of MC found in the mucosa of the small intestine and in the alveolar wall and epithelium of the respiratory tract. MC_T are identified morphologically by a scroll-rich granule structure. MC_{TC} has a scroll-poor granule structure, is the dominant type of MC in the dermis, conjunctiva, blood vessel walls, and small-intestinal submucosa. In a study in asthmatics, increased MC predominantly of the MC_{TC} type were localized to the airway smooth muscles, Fig. 1b [21].

Clinical symptoms caused by MC activation (MCA) affect cutaneous, gastrointestinal, respiratory, cardiovascular, musculoskeletal and neurological organs [1, 22–25]. Symptoms may be both acute and chronic [24–30, 31•]. Patients may also suffer from osteoporosis [32, 33].

The symptoms may vary due to MC heterogeneity, which provides a different array of protease and other mediators at different tissue sites. The distribution and triggers of different mast cell subsets are influenced by specific tissue factors and homing receptors [24–29].

An allergic disorder can be found in some cases, other less common underlying disorders are autoimmune disorders and chronic urticaria [30, 31•, 34–36].

Materials and methods

PubMed was searched using the following terms: *mast cell activation disorder*, *mast cell activation syndrome*, and *clonal mast cell*. Only English-language articles published up until May 05, 2016, were considered.

Mast cell activation

The evidence of MCA depends on at least 3 criteria:

1. Signs and symptoms compatible with mast cell mediator release in at least two organ systems.
2. Baseline or transient increase of MC-derived mediators in biological fluids (tryptase, histamine and its metabolites, prostaglandins and its metabolites).
3. Objective response to pharmacological agents that attenuate MC mediators related symptoms.

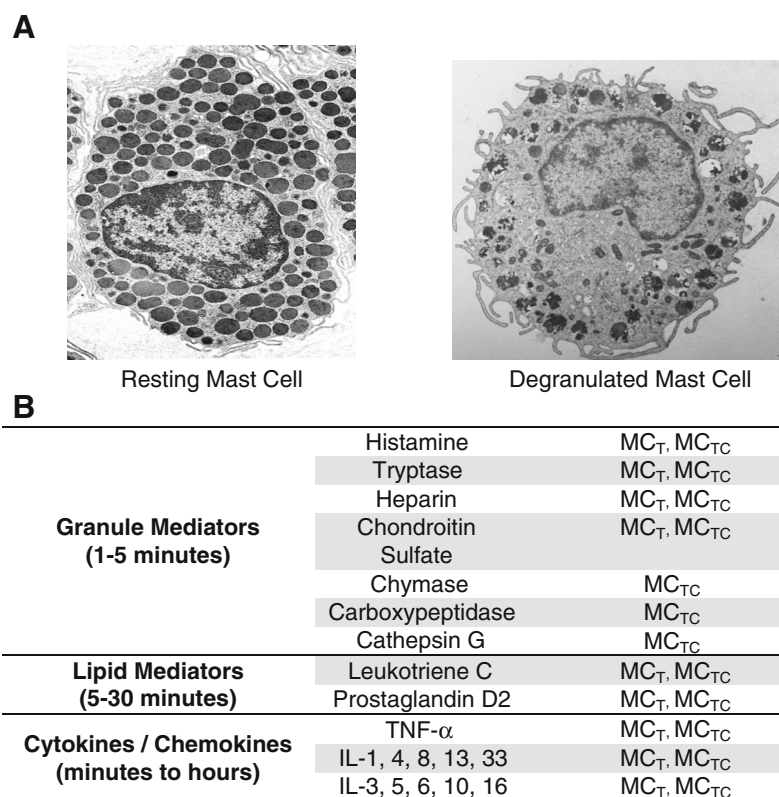


Fig. 1. (a) Mouse peritoneal mast cell at rest and after degranulation. Resting mast cell contains many granules and an intact cytoplasmic membrane. Degranulated mast cell has lost many granules and the integrity of the cytoplasmic membrane is lost presenting many gaps. [Donation from Dr Mariana Castells and Dr Daniel S. Friend] (b) Mediators released by activated mast cell phenotypes (MC_T and MC_{TC}) during the acute and delayed. IL = interleukin; TNF- α = tumor necrosis factor- α .

Table 1. Mast cell mediators considered to contribute to mast cell activation syndrome clinical symptoms

Mediator	Symptoms/signs
Histamine	Headache, hypotension, pruritus, urticaria with or without angioedema, diarrhea, anaphylaxis
Tryptase	Endothelial activation with consecutive inflammatory reactions, bleeding diathesis
Prostaglandin D ₂	Flushing, mucus secretion, bronchoconstriction, vascular instability, headache, "mixed organic brain syndrome" (poor concentration, memory loss), nausea, abdominal pain
Platelet-activating factor	Abdominal cramping, pulmonar edema, urticaria, bronchoconstriction, hypotension, arrhythmia, anaphylaxis
Cytokines (IL-1, IL-6, TNF-) and chemokines	Constitutional symptoms (fatigue), inflammation, osteoporosis
Leukotriene C ₄ and leukotriene D ₄	Mucus secretion, bronchoconstriction, edema formation, vascular instability
Chemokines	Acute inflammation and leukocyte recruitment, leukocyte migration
Renin	Cardiac arrhythmias, myocardial infarction

These criteria should be fulfilled for the diagnoses of MCA. Patients presenting MCA may have complete or partial responses to MC mediators controller medications and at times require epinephrine during severe MCA events associated with hypotension and cardiovascular collapse [16••].

Clinical symptoms

Clinical symptoms, which are associated with MCA, include cutaneous (flushing, pruritus, urticaria, angioedema), gastrointestinal (reflux, abdominal pain, cramping, diarrhea, vomiting), neuroskeletal (headache, bone pain, osteoporosis, osteopenia, bone fractures) respiratory (throat swelling, nasal congestion, shortness of breath, wheezing), cardiovascular (hypotension, hypertension, tachycardia, cardiovascular collapse) and psychiatry (mixed organic brain syndrome, depression, anxiety, short memory span).

Members of the Consensus Proposal for MCA established the most typical symptoms: Flushing, pruritus, urticaria, angioedema, nasal congestion, nasal pruritus, wheezing, throat swelling, headache, hypotension and diarrhea [16••].

MCA is clearly established when two or more of those symptoms in two or more organs are present either in acute episode or on a daily basis [5•].

Diagnostic biomarkers

Mast cells release many mediators during activation, some of them are also released by basophils. Tryptase and other proteases, such as chymase and CPA, are predominantly synthesized and released by MCs and many reports endorse that they are useful as diagnostic biomarkers. A small fraction of tryptase is synthesized and released in human basophils, approximately 0.4 % of that found in mast cells [37].

It is important to capture the elevation of tryptase levels at the time of the acute MCA event. Typically, tryptase levels increase within 30 to 60 minutes after the onset of severe symptoms of MCA, such as hypotension. The elevation of tryptase correlates with the magnitude of the event and the half life is 2-4 hours after the onset of symptoms. Patients presenting with severe hypotension or cardiovascular collapse can have elevation that persists for several days [38, 39]. Tryptase levels will be considered significantly elevated if above 20 ng/ml or if there is an increase above base line of at least 20 % plus 2 ng/ml. For example, if a patient has a basal serum tryptase level of 2 ng/ml, a significant elevation is considered at 4.4 ng/ml or above ($0.2 \times 2 + 2 + 2 = 4.4$ ng/ml) [16••].

There are other MC mediators, which are consider biomarkers, and can be measured in 24 hour urine, such as histamine or methyl-histamine, prostagladins, such as PGD₂ or its metabolite 11β-PGF_{2α}, and leukotrienes [40].

Differential diagnosis

There is no pathognomonic sign or symptom for MCA. It is very important to meet the criteria for MCA and to rule out diseases that share same sign or symptoms.

Gastrointestinal diseases (e.g., in Vipoma) associated with nausea, vomiting and diarrhea, primary skin diseases, cardiovascular disorders (e.g., in patients

with pheochromocytoma, hypotension, shock with hypotension and vasovagal syncope), various infectious diseases, intoxication (e.g., in Scombroid poisoning), endocrine disorders (e.g., in Pheochromocytoma, hyper- and hypothyroidism), diverse neoplasms (e.g., in the Carcinoid), and conditions associated with neurological and psychiatric symptoms (depression, anxiety) [16••].

Tryptase should be determined, as well as other available MC biomarkers, such as metil-histamine and prostaglandin in 24 hour urine, at base line and during acute episodes.

Local release of mast cell mediators may occur without systemic repercussion, and basophils may be responsible for symptoms without systemic elevation of tryptase. In inflammatory bowel diseases, local mast cell degranulation has been demonstrated and is the site of inflammation and thought to be partially responsible for the symptoms. Sodium cromoglycate has been helpful to patients with IBD, supporting a role for MC and MC mediators [41].

Scombroid syndrome can occur after the ingestion of sea food, fish, wine, and soy sauce and relates to the increased histamine content [42].

Some of the possible differential diagnoses of MCA and their tests for investigation are in Table 2.

Mast cell activation syndromes: classification and diagnostic approach

The current classification includes three means categories: primary, secondary, and idiopathic (Table 3 and Fig. 2a).

Primary (cutaneous mastocytosis, systemic mastocytosis, monoclonal mast cell activation syndrome and local MC tumors)

- 1) Cutaneous mastocytosis (CM) is present when the skin is the only affected organ. Recent data indicates that children and adults with urticaria pigmentosa can carry Kit mutation. The new classification from the Consensus Report of the European Competence Network on Mastocytosis in 2016, includes maculopapular CM, diffuse CM and mastocytomas [44]. Telangiectasia Macularis Eruptiva Perstans is considered a rarer entity. Maculopapular CM is by far the most common, and the lesions can be heterogeneous or monomorphic [45••]. In children with monomorphic presentation, there is a tendency of the lesions to persist to adulthood, and to be associated with systemic involvement. The majority of polymorphic presentation in children resolve around puberty. In a cohort of 50 children with CM, 42 % carried an exon 17 kit mutation, indicating that the presence of kit mutation does not preclude the resolution of lesions in puberty. Patients with CM with an extensive skin mast cell burden can have local release of mediators, which are absorbed to blood vessels and release systemically inducing systems and distant organs [44, 46]. In contrast, most adults with CM have an underlying systemic SM and should undergo a bone marrow biopsy regardless of the presence of associated systemic symptoms of mediator release [47]. Conversely, 80 % of SM patients have cutaneous disease that manifests as urticaria pigmentosa [44, 48].

Table 2. Selected differential diagnosis of mast cell activation disorders

Differential Diagnosis	Useful Test(s) in Investigation
Flushing	
Menopause	FSH, LH, estrogen
Carcinoid syndrome	24-Hour urine 5-hydroxyindoleacetic acid
Pheochromocytoma	24-Hour urine fractionated catecholamines and metanephrines
Medullary carcinoma of the thyroid	Serum calcitonin
Cardiovascular (presyncope/syncope, tachycardia, hypotension)	
Postural tachycardia syndrome (POTS)	Tilt table test
Autonomic dysfunction	Orthostatic drop in blood pressure
Cardiovascular diseases (arrhythmia)	ECG
Respiratory symptoms (throat tightness, stridor, wheezing)	
Asthma	Pulmonary function tests
Vocal cord dysfunction	Laryngoscopy, spirometry
Hereditary and acquired angioedema	C4, C1q, C1 inhibitor antigenic and functional levels
ACE inhibitor-associated angioedema	Plasma bradykinin ^a
Gastrointestinal symptoms (diarrhea, abdominal cramping)	
Primary bowel disease (irritable bowel syndrome, inflammatory bowel disease)	Endoscopy and biopsy
Neuroendocrine tumors	Serum vasoactive intestinal peptide
Other	
Panic attack	Psychiatric consultation

ACE angiotensin-converting enzyme; FSH follicle-stimulating hormone; LH luteinizing hormone

^aPlasma bradykinin is elevated in ACE inhibitor-associated angioedema and hereditary and acquired angioedema, whereas it is normal in mast cell-related angioedema. 16 Test not currently available. Diagnosis of ACE inhibitor-associated angioedema is based on history [Adapted from Picard [43]] Reprinted from Clinical Therapeutics, Vol 35/Issue 5, Matthieu Picard, Pedro Giavina-Bianchi, Veronica Mezzano, and Mariana Castells, Expanding Spectrum of Mast Cell Activation Disorders: Monoclonal and Idiopathic Mast Cell Activation Syndromes, 548-562, Copyright 2013, with permission from Elsevier

- 2) Systemic mastocytosis (SM) is defined by the presence of major and/or minor criteria. Major criteria include the presence of MC aggregates containing 15 or more MC together in bone marrow or any extra cutaneous organ. There are four minor criteria including: The presence of abnormal morphology in 25 % of MC with spindle shapes, the expression of T cell activation marker CD25, the presence of KIT mutation D816v and tryptase elevation above or equal to 20 ng/ml (Fig. 3a, b, c) [50].
- 3) The algorithm (Fig. 2b) leads to the subvariants of SM: Indolent, aggressive, associated with a hematologic non-mast cell lineage disease and mast cell leukemia. In the category of indolent systemic mastocytoses, a new subgroup of patients has been described with hymenoptera anaphylaxis. These patients have low mast cell burden,

Table 3. Mast cell activation syndrome classification

Primary :	Cutaneous mastocytosis Systemic mastocytosis Mast cell sarcoma Mastocytoma Monoclonal mast cell activation syndrome
Secondary:	IgE-mediated hypersensitivity reactions Drugs Mast cell hyperplasia
Idiopathic:	“Idiopathic anaphylaxis” Idiopathic mast cell activation syndrome

some with urticaria pigmentosa and few mast cell mediator related symptoms [35, 51, 52].

- 4) Monoclonal mast cell activation syndrome (MMAS) is a new category of MC clonal disorder associated with the presence of clonal, CD25 positive MC in the bone marrow without MC aggregates and the presence of KIT D816v mutation [33].

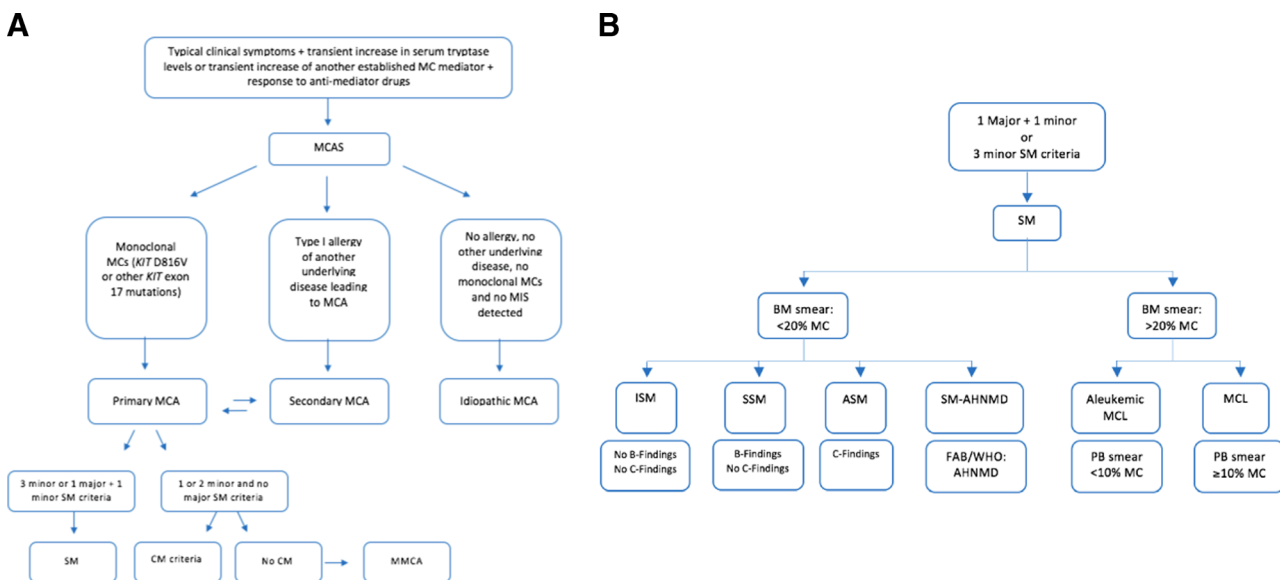


Fig. 2. (a) Diagnostic algorithm in patients with suspected MCA disorder. [Adapted from Valent [16••], Copyright © 2011 Karger Publishers, Basel, Switzerland] (b) Algorithm for the subvariants of systemic mastocytosis (SM). Using criteria defining the spread of disease (B-Findings) and the aggressiveness of the mast cell infiltrate (= grading criteria = C-Findings) as well as WHO criteria for the definition of non MC haematopoietic neoplasms, the subvariant of SM and thus the final diagnosis, is established. AHNMD: Associated clonal haematological non-MC-lineage disease; SM-AHNMD: Systemic mastocytosis associated clonal haematological non-MC-lineage disease; ISM: Indolent systemic mastocytosis; SSM: Smouldering systemic mastocytosis; ASM: Aggressive systemic mastocytosis; MCL: Mast cell leukaemia.

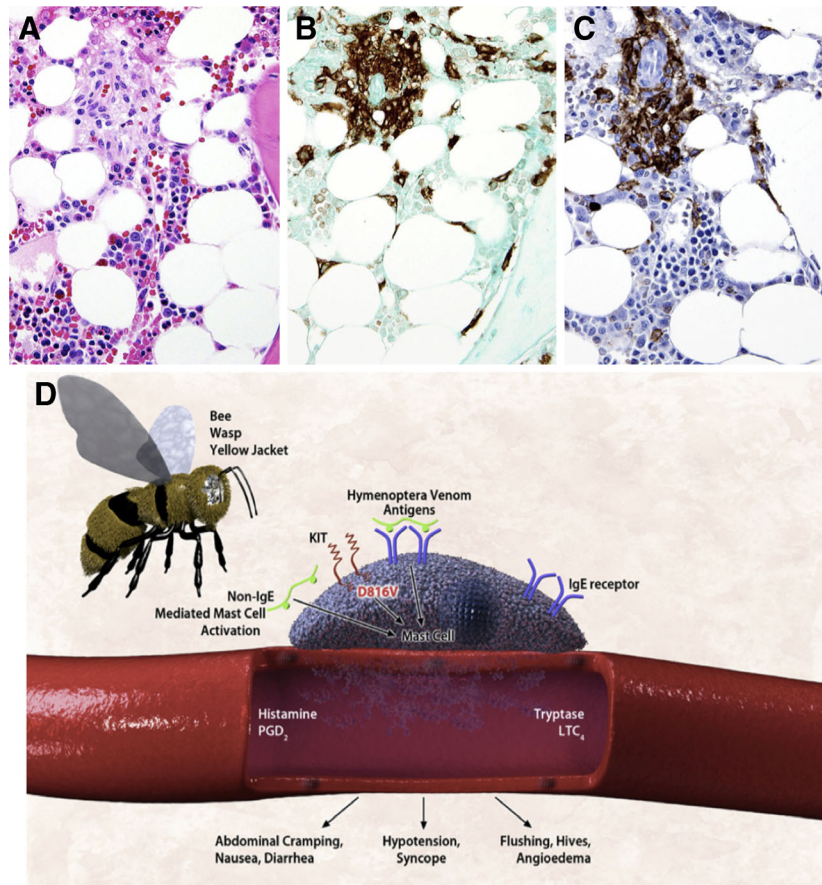


Fig. 3. (a) Bone marrow biopsy of a patient with SM and hymenoptera anaphylaxis showing a perivascular aggregate of mast cells with ovoid to spindle-shaped nuclei and abundant pale cytoplasm (H&E). (b) Immunohistochemistry for KIT (CD117) is positive in the aggregate of mast cells and also highlights scattered single spindle-shaped mast cells. (c) The mast cells show aberrant membranous staining for CD25 (all images original magnification 400). H&E, Hematoxylin and eosin. (d) Illustration of the release of mast cell mediators leading to anaphylaxis in response to hymenoptera venom in patients with clonal mast cell disease. LTC₄, leukotriene C₄; PGD₂, prostaglandin D₂. [Adapted from Castells [49]] Reprinted from The Journal of Allergy and Clinical Immunology: In Practice, Volume 3/Issue 3, Mariana C. Castells, Jason L. Hornick, and Cem Akin, Anaphylaxis After Hymenoptera Sting: Is It Venom Allergy, a Clonal Disorder, or Both?, 350-355, Copyright 2015, with permission from Elsevier.

- 5) Local MC tumors are divided into mastocytoma and MC sarcoma. Mastocytoma occur in 10–35 % of the cases of cutaneous mastocytosis in children, and present as one or several lesions that resemble UP but are larger, up to several centimeters in diameter. Solitary mastocytomas are present at birth or develop within one week. Flushing can be present and Darrier's sign is typically positive, rarely present with diarrhea, and association with visceral involvement or systemic disease is rare. No familial history was found in mastocytomas. MC sarcoma is a form of mastocytosis that is exceedingly rare and aggressive presenting as a solitary mass or tumor. The composition of the mass is of large atypical MC, multinucleates and with epithelioid features. Most of MC sarcomas are imatinib-resistant due to Kit D816v mutation [53].

Secondary

Secondary causes of MCA should be evaluated in patients to address their potential treatment, such as hypo- and hyperthyroidism or atopic conditions [16••]. Reactions may be related to IgE-mediated hypersensitivity reactions, such as allergies to food, insects, and drug-induced anaphylaxis. MCA is also correlated to drug-induced reactions to vancomycin, opioids, and taxanes.

Mast cell hyperplasia is the presence of increased MC numbers in different tissue and organs without MC aggregates and in most cases is reactive to local inflammation [54]. Mast cell hyperplasia can be associated with infections, neoplasia, inflammatory reactions, lymphoproliferative diseases and bone marrow suppression. In these diseases it is possible that an excess of stem cell factor can induce the MC hyperplasia [16••, 55, 56].

Idiopathic (IA and IMCAS)

- 1) “Idiopathic anaphylaxis” (IA) should only be considered after an extensive diagnostic investigation and an inability to identify a trigger for a patient’s allergy. The symptoms of idiopathic anaphylaxis are no different from those in cases where the trigger is known and, as with all cases of anaphylaxis, idiopathic anaphylaxis has the potential to be life threatening.
- 2) Idiopathic mast cell activation syndrome (IMCAS) or non-clonal mast cell activation syndrome should be considered if: The patient has signs and symptoms of MCA in at least two organ systems; rule out medical disorders that may explain symptoms (e.g., carcinoid, pheochromocytoma, gastrinoma, VIPoma); no evidence of mast cell clonality; elevated MC mediator (tryptase, N-methylhistamine, PGD₂/11β-PGF₂a) and good response to medications that block MC mediators. One third of IMCAS patients experience complete resolution of symptoms with treatment, while one third have a major response and one third a minor response to treatment [43]. Patients with IMCAS never have CM [57]. It seems to affect more women, and it has been reported that out of 32 patients, 22 were women [31•]. In Table 4 is a comparison of SM, MMAS, IMCAS and IA [48].

Treatment

The response to therapy with histamine receptor ‘blockers’ (inverse agonists) and other MC controller medications, such as cromolyn, leukotriene receptor blockers, cyclooxygenase inhibitors, glucocorticosteroids, 5-lipoxygenase inhibitors, or antagonists of certain cytokines is considered evidence of the participation of MC [58, 59]. There is no cure at this time for clonal MC disorders, but it is possible to have a complete or partial response to MC mediator controller medications.

When MCA is strongly suspected with laboratory evidence of MC mediator release, medical treatment using a standard stepwise approach to address each symptom and its systemic impact can provide excellent results (Table 5) [43].

Table 4. Comparison between systemic mastocytosis (SM), monoclonal mast cell activation syndrome (MMCAS), idiopathic mast cell activation syndrome (IMCAS) and idiopathic anaphylaxis (IA)

Clinical and Laboratory Features	SM	MMCAS	IMCAS	IA
Multifocal mast cell aggregates	Present ^a	Absent	Absent	Absent
D816V <i>KIT</i> mutation	Present ^b	Present ^c	Absent	Absent
Aberrant CD25 expression on bone marrow mast cells	Present	Present ^c	Absent	Absent
Baseline tryptase	Elevated ^d	Normal or elevated	Normal or elevated	Normal ^e
Baseline 24-hour urine methylhistamine or Prostaglandin D2/11 -PGF _{2α}	Elevated	Normal or elevated	Normal or elevated	Normal
Urticaria pigmentosa	Present or absent	Absent	Absent	Absent
Mediator release symptoms	Present	Present	Present	Present
Response to antimediator therapy	Good	Good	Good	Variable

[Adapted from Picard [43]] Reprinted from Clinical Therapeutics, Vol 35/Issue 5, Matthieu Picard, Pedro Giavina-Bianchi, Veronica Mezzano, and Mariana Castells, Expanding Spectrum of Mast Cell Activation Disorders: Monoclonal and Idiopathic Mast Cell Activation Syndromes, 548-562, Copyright 2013, with permission from Elsevier

^aMajor diagnostic criterion for SM; not present in all patients with SM

^bOther *KIT* mutations have also been associated with SM

^cMay require enrichment of bone marrow mast cells

^dSerum tryptase 20 ng/mL is a minor criterion for SM; not present in all patients with SM

^eSerum tryptase typically elevated above normal range or more than 20 % + 2 ng of baseline at the time of acute episode

Triggers

Identification and avoidance of triggers that lead to MCA is of main importance for symptom control.

It is known as the most common trigger for symptoms for alcohol and heat [5•]. Another trigger that is frequently reported is Hymenoptera stings, and it can be the first manifestation of MCA [60]. Venom immunotherapy (VIT) should be offered to patients during an investigation if venom-specific IgEs are present [35, 60–62]. The buildup of VIT may be difficult due to the systemic reactions, which are more frequently in patients with elevated baseline serum tryptase [63, 64]. Reports of fatalities have been documented in patients with mastocytosis who were stung by hymenoptera after stopping VIT and current recommendations promote life-long VIT [62].

General anesthesia and procedures including the use of contrast media can also trigger reactions in MCA patients [47]. Current recommendations strongly endorse the use of premedication including H1 and H2-blockers, leukotriene antagonists, and corticosteroids [33].

Treatment of acute episodes

Patients with anaphylaxis and elevated baseline serum tryptase concentration (11.4 ng/mL) are at risk for serious events with cardiovascular collapse and potentially life-threatening episodes. These patients should carry several autoinjectable doses of epinephrine at all times [33, 65, 66]. The administration of epinephrine should occur with the patient in a supine position, and injected

Table 5. Stepwise prophylactic treatment approach for MC mediators-related symptoms

System/Symptoms/Step No.	Drugs
Skin: Pruritus, flushing, urticaria, angioedema, dermatographism	
1	H1-blockers ^a H2-blockers
2	Leukotriene antagonists ^b
3	Aspirin ^c
4	Ketotifen
Gastrointestinal: Diarrhea, abdominal cramping, nausea, vomiting	
1	H2-blockers
2	Cromolyn sodium
3	Proton pump inhibitors
4	Leukotriene antagonists ^b
5	Ketotifen
Neurologic: Headache, poor concentration and memory, brain fog	
1	H1- and H2-blockers
2	Cromolyn sodium
3	Ketotifen
Cardiovascular: Pre-syncope, syncope, tachycardia	
1	H1- and H2-blockers
2	Corticosteroids ^d
3	Omalizumab
Pulmonary: Wheezing, throat swelling	
1	H1- and H2-blockers
2	Leukotriene antagonists ^b
3	Corticosteroids (including inhaled corticosteroids) ^d
4	Omalizumab
Anaphylaxis	
Acute	Epinephrine (intramuscular)
1	H1- and H2-blockers
2	Corticosteroids ^d
3	Omalizumab
Naso-ocular: Nasal stuffiness, nasal pruritus, conjunctival injection	
1	H1-blockers (including topical formulations)
2	Topical corticosteroids
3	Cromolyn sodium (topical formulation)

[Adapted from Picard [43]]

^aNonsedating second-generation H1-blockers preferred^bMontelukast, zafirlukast, or zileuton^cEspecially useful in patients with treatment-resistant flushing and elevated urinary prostaglandin D2^dSuggested initial dose of 0.5 mg/kg/d tapered over 1 to 3 months. For recurrent anaphylactic episodes (1/mo) unresponsive to corticosteroids or dependent on corticosteroids for control

in the lateral aspect of the quadriceps intramuscularly. Several doses may be needed for refractory cases. Fluid resuscitation, H1 and H2-blockers and corticosteroids (0.5–1 mg/kg) should be considered [67].

Associated conditions: hymenoptera anaphylaxis, familial tryptasemia, Postural Orthostatic Tachycardia Syndrome and Ehlers-Danlos syndrome

Hymenoptera anaphylaxis

Patients with mastocytosis may present severe systemic reactions to hymenoptera venom (HV). Patients with primary MCA and HV anaphylaxis are predominantly males without cutaneous manifestations and syncope with hypotension in the absence of urticaria and angioedema. Patients with primary MCA and HV anaphylaxis must be submitted to lifelong VIT, in order to prevent further potentially fatal severe reactions [68].

It is unknown what is the precise mechanism of increased susceptibility to HV anaphylaxis in mastocytosis. Potential explanations include the following: Increased number of MC amplifying the severity of the reaction resulting from higher MC mediator release, perivascular location of the MC providing direct access to the intravascular compartment, D816V-mutant KIT amplifying the IgE-mediated reaction and additive direct (none IgE-mediated) MC activating properties of the hymenoptera venom, including phospholipase A2 (Fig. 3d) [49••].

Familial hypertryptasemia

Usually MCA behaves as a nonheritable condition. Sabato et al. reported a 3-generation family in whom seven family members have hypertryptasemia, with basal tryptase levels of greater than 20 ng/mL (median, 37 ng/mL; range, 25.5–62.7 ng/mL). Out of these seven family members, four had recurrent episodes of abdominal cramping and diarrhea for several years and after investigation they were diagnosed with IMCAS [69].

Lyons reported 33 patients divided in nine families with increased basal serum tryptase levels. Among these patients, the clinical symptoms consistent with chronic and episodic mast cell degranulation were: Atopy 94 %, gastrointestinal 85 %, cutaneous in 75 %, neuropsychiatric 73 %, and connective tissue 70 %. None of the patients presented conclusive criteria for SM or monoclonal mast cell activation [70].

Postural Orthostatic Tachycardia Syndrome

Postural tachycardia syndrome (POTS) is a disabling condition that commonly affects otherwise normal young females. It is characterized by symptoms of fatigue, tachycardia, shortness of breath, and even syncope on standing [71]. Activated MC may provide a source of circulating vasodilators in a subset of patients with hyperadrenergic POTS [72]. MCA patients who have POTS present flushing, shortness of breath, headache, GI symptoms triggered by standing, exercise, a premenstrual cycle and intercourse. Patients improve clinically when treated with H1 and H2 receptor blockers, indicating that histamine may play an important role in a subset of POTS patients. MCA should be considered in patients with POTS presenting with flushing [72].

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) includes a group of heterogeneous disorders in which inherited abnormalities of collagen induce symptoms associated with skin hyperextensibility, joint hypermobility, and fragile connective tissue [73]. The characteristics of patients with EDS type III (EDS-Hypermobility) include autonomic desregulation, palpitations, lightheadedness, chest pain, presyncope, and syncope [74]. Exercise, meals, and a hot environment, in addition to prolonged standing can trigger symptoms [75, 76]. Autonomic tests, such as the TILT table test, are consistent with disturbed sympathetic cardiovascular control. Recent studies of autonomic symptoms/function and quality of life confirm a high prevalence of orthostatic symptoms and orthostatic intolerance in these patients [77].

Eighteen percent of POTS patients met criteria for EDS, compared to a 0.02 % prevalence in the general population; EDS type III is the most common disorder associated with POTS [73, 78].

Further studies are necessary to understand the interaction between symptoms associated with POTS and EDS-Hypermobility. Connective tissue abnormalities in EDS may lead to vascular instability and predispose patients to blood pooling in the lower extremities and orthostatic intolerance [74, 79].

Patients experiences and perceptions

Because the quality of life is diminished in patients with MCA, attempts have been made to further understand the patients' perceptions and views through validated questionnaires. Members of a Consensus Proposal from USA and EU indicated the need for increased expert physicians on MCA and in referral centers [16••]. The panel underscored the importance of developing effective therapies to address all the presentation and diseases associated with MCA. Increasing awareness and more information are highly desirable.

Jennings et al. evaluated 379 patients and their perceptions on living with an MCD. More than 60 % of respondents were affected either moderately or extremely regarding their need for coping with unpredictability of symptoms, gastrointestinal problems, and fatigue [80•].

Conclusion

MCA disorders are classified as primary or clonal disorders associated with KIT mutation and MC hyperplasia, secondary to other underlying diseases and idiopathic without MC hyperplasia but with increased symptoms of MCA.

Diagnoses of MCAS rely in three criteria: Symptoms related to mast cell mediators, objective response to pharmacological agents that attenuate MC mediator related symptoms and mast cell mediators elevated in biological fluids, such as tryptase. Once MCAS is identified, genotyping for Kit mutation through a bone marrow biopsy will distinguish the clonal from non-clonal disease. Symptoms can be common to other diseases, making the diagnoses difficult with patients suffering many years before a diagnosis is made. Major complications of SM involves gastrointestinal symptoms, osteoporoses and bone fractures.

The most common clonal form of MCAS are cutaneous mastocytosis and indolent systemic mastocytosis with normal life span and symptoms of MCAS.

A new type of mastocytosis has recently emerged in patients with anaphylactic reactions to hemynoptera venom, a majority of these patients present an underlying systemic mastocytosis.

The quality of life of MCAS patients is decreased by the severity and unpredictability of the symptoms, which may limit their family, social, and professional interactions.

Research is needed to further understand MCAS, its mediators and to pursue pharmacological controllers of MCAS.

Compliance with Ethical Standards

Conflict of Interest

Dr. Rafael Bonamichi-Santos declares that he has no conflict of interest.

Dr. Mariana Castells declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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