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Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders?

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Abstract

Introduction: An increasing number of patients present with multiple symptoms affecting many organs including the brain due to multiple mediators released by mast cells. These unique tissue immune cells are critical for allergic reactions triggered by immunoglobulin E (IgE), but are also stimulated (not activated) by immune, drug, environmental, food, infectious, and stress triggers, leading to secretion of multiple mediators often without histamine and tryptase. The presentation, diagnosis, and management of the spectrum of mast cell disorders are very confusing. As a result, specialists have recently excluded neuropsychiatric symptoms, and made the diagnostic criteria stricter, at the expense of excluding most patients.

Areas covered: A literature search was performed on papers published between January 1990 and November 2018 using MEDLINE. Terms used were activation, antihistamines, atopy, autism, brain fog, heparin, KIT mutation, IgE, inflammation, IL-6, IL-31, IL-37, luteolin, mast cells, mastocytosis, mediators, myalgic encephalomyelitis/chronic fatigue syndrome, mycotoxins, release, secretion, tetramethoxyluteolin, and tryptase.

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Declaration of interest

TC Theoharides is on the Scientific Advisory Board of The Mastocytosis Society (TMS, www.tmsforacure.org) TC Theoharides is the Scientific Director of Algonot, LLC, which has developed flavonoid containing dietary supplements. TC Theoharides is the inventor of US patent nos. 6,635,625; 6,641,806; 6,645,482; 6,689,748; 6,984,667; 7,906,153; 8,268,365; 9,050,275; and 9,76,146, as well as EPO 1365777 covering the use of proteoglycans and flavonoids for the treatment of mast cell-related and inflammatory diseases. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

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Expert opinion: Conditions associated with elevated serum or urine levels of any mast cell mediator, in the absence of any comorbidity that could otherwise explain such increases, should be considered mast cell activation disorders, or better yet be collectively termed ‘Mast Cell Mediator Disorders (MCMD).’ Emphasis should be placed on the identification of unique mast cell mediators, and development of drugs or supplements that inhibit their release.

Keywords

Activation; antihistamines; autism spectrum disorder; brain fog; KIT mutation; cytokines; IgE; inflammation; IL-6; IL-37; luteolin; mast cells; mastocytosis; mediators; myalgic encephalomyelitis/chronic fatigue syndrome; mycotoxins; tetramethoxyluteolin; tryptase

1. Introduction

Over the last few years, there has been an unusual increase in atopic diseases, including allergies, asthma, eczema, rhinitis, and food sensitivities. In addition, there have been numerous cases of patients presenting with symptoms consistent with allergies, and/or inflammation, affecting many organs, but no recognizable trigger or too many non-allergic triggers. These symptoms (Table 1) originate from mediators secreted (released) from mast cells and include flushing, pruritus, hypotension, gastrointestinal complaints, headaches, irritability, malaise, memory loss, and neuropsychiatric issues. As a result, a number of different names have been proposed to capture these symptoms such as mast cell diseases or mast cell disorders (MCD) and mast cell activation diseases or mast cell activation disorders (MCAD).

Unfortunately, these are many confusing aspects both in the naming and diagnosis of such disorders. First, the term ‘activation’ is typically reserved for activation of receptors or enzymes while ‘stimulation’ is used for cells. Second, stimulation of mast cells may imply proliferation without secretion of all or even any mast cell mediators as in the case of mast cell sarcoma. Next, the term ‘secretion’ is usually reserved for mediators stored inside secretory granules, while the term ‘release’ is used for both pre-stored and newly synthesized mediators. Be it as it may, release of mast cell mediators can occur in many physiologic and pathologic settings. To make matters worse, there are a number of other diseases that mimic and/or are comorbid with diseases involving mast cells (Table 2). As a result, affected patients often go for 10–20 years and as many physicians of different specialties before a diagnosis is made, by which time they have been prescribed numerous medications, often with severe drug interactions that further complicate their presentation and course of their disease.

2. Mast cell biology

Mast cells are immune cells derived from hematopoietic precursors and mature in tissue microenvironments [1]. Mast cells are critical for the development of allergic reactions [2], but also act as sensors of environmental and psychological stress [3,4]. Perivascular mast cells were shown to probe cutaneous blood vessels by extending philopodia through endothelial gaps and capture immunoglobulin E (IgE) from blood vessels [4], a process that might also allow mast cells to sense and capture other circulating molecules. Mast cells also

participate in the innate immune system (host defense against infectious pathogens, neutralization of toxins) and in the adaptive immune response [5–9], but also in antigen presentation [10,11] regulation of T cell responses [12–14], even in the absence of antigen presentation [15], autoimmunity [16], and inflammation [17–19].

Mast cells are located in tissues that interface with the external environment [20] and are stimulated primarily by IgE-dependent reactions (allergen). In addition to allergens, mast cells are also stimulated by a variety of different triggers (Table 3) that include bacteria, drugs, foods, fungi, heavy metals, organophosphates, viruses, and 'danger signals' [2], as well as certain neuropeptides including corticotropin-releasing hormone (CRH) [21], neurotensin (NT) [22,23], and substance P (SP). Both NT [24,25] and SP [26–29] are known to participate in inflammatory processes. Many cationic drugs have now been shown to stimulate mast cells through activation of the low affinity G-protein-coupled receptor MRGPRX2 [30]. Mast cells commonly respond to non-allergic triggers leading to mediators may also be released selectively without degranulation making it difficult to identify these mast cells with routine histology [31] (Table 4).

Upon stimulation, mast cells secrete preformed mediators (Table 5) such as β-hexosaminidase (β-hex), histamine, tumor necrosis factor (TNF), and tryptase through rapid (1–5 min) degranulation. Mast cells are the only cell type that stores preformed TNF [32], which is rapidly secreted and influences T cell recruitment and activation [33–35]. Mast cells also release newly synthesized phospholipid products such as prostaglandin D_2 (PGD_2) and leukotrienes [36–38]. Mast cells also secrete numerous *de novo* synthesized protein mediators typically 6–24 h after stimulation such as cytokines [39], chemokines (TNF, CCL2, CCL8), and peptides hemokinin-1 (HK-1), and renin [19,40] (Table 4). Mast cell-derived CCL2 and CXCL8 enhance recruitment of other immune cells to the site of inflammation [41].

Moreover, corticotropin-releasing hormone (CRH or factor, CRF) is also synthesized by mast cells [42] implying that it could have autocrine effects [17,43]. In particular, CRHR-1 is expressed on human cultured mast cells, activation of which induces production of vascular endothelial growth factor (VEGF) without tryptase [21].

Mast cells can secrete IL-31, which is particularly pruritogenic [44], as well as additional 'danger' signals [45] (Table 4). Mitochondrial DNA (mtDNA) [34,46] can lead to auto-inflammatory responses [47–50], augment allergic responses [51], and has direct neurotoxic effects [52]. We had reported that mtDNA is increased in the serum of children with autism spectrum disorder (ASD) [53]. Another key danger signal is the alarmin IL-33 [54], which is secreted by fibroblasts and endothelial cells, and has been implicated in many allergic [55] and inflammatory [56] diseases. IL-33 augments the effect of IgE on secretion of histamine from mast cells and basophils [54,57]. It is interesting that the most widely used herbicide glyphosate induces IL-33 expression and airway inflammation [58].

We showed that IL-33 augments the ability of SP to stimulate secretion of VEGF from human mast cells without degranulation [59]. We recently also reported that SP and IL-33, when administered in combination, lead to an impressive increase in the gene expression and

secretion of TNF [60] and IL-1β [61] from cultured human mast cells. Mast cells can secrete IL-33 [62,63], as well as the SP-related peptide HK-1 [64], implying autocrine augmentation. Moreover, tryptase secreted from mast cells acts on extracellular IL-33 and generates mature, more active IL-33 [65], which then stimulates mast cells to secrete IL-1β, which in turn stimulates mast cells to secrete IL-6 [66]. In addition, mast cell-derived TGFβ promotes the development of Th17 cells and mast cells can also secrete IL-17 themselves [67].

Stimulated mast cells can secrete their numerous bioactive mediators [19,68,69] utilizing different signaling [70–73] and secretory [70,74] pathways. One important pathway is that of mammalian target of rapamycin (mTOR) [75], which we have shown to be stimulated by SP in human cultured mast cells [76]. The ability to secrete multiple mediators allows mast cells to actively interact with other cell types in their surrounding environment, especially T cells [77,78]. It is interesting that secretion of mast cell mediators have been shown to be regulated by a circadian clock [79,80].

Each mediator could lead to specific clinical features. For instance, histamine is associated with headaches, hypotension, and pruritus; tryptase with inflammation and fibrinogen lysis; cytokines and chemokines with constitutional symptoms of generalized inflammation and fatigue, PGD_2 with flushing, and leukotrienes with bronchoconstriction. As a result, mast cell-derived mediators could contribute to the pathogenesis of not only allergic diseases, asthma and mastocytosis [2], but also in atopic dermatitis, psoriasis, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [81], fibromyalgia syndrome (FMS) [82], coronary artery disease, and obesity [83], as well as ASD [17,50,84].

The severity of symptoms depends on many factors, such as the capacity of mast cells to secrete mediators, the levels of circulating IgE, the presence of cytokines and chemokines [85], especially IL-33 [59], as well as the co-existence of high-risk conditions, such as stimulation by hymenoptera venom(s) especially in patients suffering from mastocytosis [86–89]. Reactivity to wasp stings could lead to anaphylaxis, characterized by the sudden onset of severe flushing, swelling of the throat, bronchoconstriction, and hypotension that may progress to death [90]. Basophils also participate in allergic and other inflammatory reactions in-ways somewhat similar to that of mast cells, except that their main trigger is IgE and they do not contain tryptase [91,92]. Various assays have been proposed to document the involvement of basophil activation [93,94], via identification of CD63 and CD203c [93–95].

3. Classification and diagnostic features of mast cell disorders

This topic is quite confusing because of the use of different terminology by various specialists and consensus groups. For instance, the terms ‘mast cell diseases,’ ‘mast cell disorders,’ and ‘mast cell syndromes’ are often used interchangeably. In this review, the term ‘mast cell disorders’ is used as it includes many variants or subtypes.

Disorders involving mast cells [96,97] have been traditionally classified into three general categories: primary, secondary, and idiopathic [98,99]. However, new information on the genetic and epigenetic causes of the occurrence and severity of the symptoms [100] requires

a new approach to the understanding and classification of these disorders as shown in Table 6. Historically, 'primary' has been used to imply that these disorders are caused by genetic and/or epigenetic alterations leading to functional consequences in proliferation of mast cells in the bone marrow, skin, or other tissues/organs.

3.1. Clonal mast cell proliferation disorders

3.1.1. Systemic mastocytosis—Systemic mastocytosis (SM) is defined by mast cell involvement of at least one extracutaneous tissue typically in the bone marrow, if certain criteria are fulfilled [101]: one major criterion of mast cell clusters in bone marrow biopsy and one minor criterion (e.g. elevated basal serum tryptase, spindle-shaped mast cells), or three minor criteria established by the World Health Organization (Table 7) [102]. However, these criteria are strongly based on the presence of a 'gain-of-function' mutation in the gene *KIT* at codon 816 (D816V) or other codons nearby. Systemic mastocytosis can be characterized as (a) indolent, (b) aggressive, or (c) associated with a hematologic non-mast cell lineage disease. Sometimes a single bone marrow biopsy may miss mast cell clusters. In our study, only 17% of patients had evidence in one biopsy, but 83% of patients had evidence of mastocytosis when two iliac crest biopsies are taken [103].

Mast cells should be identified by immunohistochemistry for both tryptase and KIT (CD117), the surface receptor for stem cell factor (SCF), because KIT indicates the presence of all mast cells whether they have degranulated or not while the presence of tryptase or lack thereof indicates the degree of degranulation. CD117 is considered the marker of choice for the GI tract, especially in the portal triads. Flow cytometric immunophenotyping using antibodies against tryptase, CD117 (KIT), and CD25 could be performed in peripheral blood in suspected cases before advancing to bone marrow biopsies (Figure 1). Mast cells are low at bone marrow smears, and many cells are damaged making it difficult to identify abnormal mast cells.

Typically, patients are considered candidates for bone marrow biopsy is: (a) Tryptase >20 ng/ml; (b) have a history of previous hypotensive episodes and/or syncope; (c) diffuse cutaneous mastocytosis (CM) in adult patients; (d) unexplained anaphylaxis or explained anaphylaxis provoked with hymenoptera stings even when specific IgE testing to hymenoptera is negative [104–106]. Bone marrow or peripheral mast cells should then be tested for the presence of the *KIT* mutation D816V, which is present in over 90% of patients with SM [107]: (e) Insect-induced anaphylaxis with symptoms different than those of SH [108]; (f) Presence of unexplained osteoporosis, hepatomegaly, and splenomegaly (suspicion for an aggressive variant of SM) [104]; (g) Abnormalities on peripheral blood count in patients with a MCAD (several hematologic non-mast cell lineage such as chronic myelomonocytic leukemia and myelodysplastic syndrome, but also other myeloproliferative neoplasms and lymphoproliferative diseases) [109] (Figure 1).

The most common mutation found in patients with SM is the point mutation located at codon 816 of *KIT* which affects mast cells: (a) It promotes the autonomous growth and expansion of the neoplastic mast cells [110]; (b) It can trigger mast cells to release IL-6 at high concentrations of SCF [111]. The D816V mutation may also be expressed in individuals in whom criteria for SM are not fulfilled [86,99,106,112–114], in which cases,

the patients are considered to have monoclonal mast cell activation syndrome (MMAS) (see below). There are some additional, but not as common, functionally activating mutations of KIT (e.g. D419H, V560G), which do not induce detectable morphological alterations of affected mast cells; these mutations can still influence the evolution of the disease and/or the manifestation of certain symptoms [59].

Some other gene mutations (e.g. *FIP1L1-PDGFRA*) result in a constitutively activated platelet-derived growth factor receptor-α (PDGFRA) and have been associated with a primary eosinophilic disorder. In one study, 10 (56%) of 19 patients with systemic mast cell disease associated with eosinophilia carried this specific mutation, which when present is indicative of underlying systemic mastocytosis [115].

3.1.2. Cutaneous mastocytosis—In this subcategory, affected skin most commonly presents as urticaria pigmentosa (UP) or diffuse CM, and less frequently as bullous CM or solitary mastocytoma [96,116]. Different from adults with CM, bone marrow biopsy is not recommended for children [117,118]. It is generally considered that pediatric CM regresses by puberty in most children [116], but there have not been any systematic longitudinal studies to prove this point. However, increased serum baseline total tryptase identifies children at risk for SM [119], as does the presence of maculopapular cutaneous mastocytosis [120] [121] or detection of *KIT D816V* in peripheral blood [122]. It is interesting that *KIT D816V* is not present in most skin lesions suggesting that there may be committed stem cells outside the bone marrow. In this case, the molecules triggering mast cell proliferation in the skin may be NGF [123], RANTES [124], or even CRH acting on precursors in the hair follicle mesenchyme [125]. It is interesting that new UP lesions in children often occur in areas of trauma.

Telangiectasia macularis eruptive persistans is a variant of CM, not associated with urticaria [126].

3.1.3. Monoclonal mast cell activation disorder—This subcategory is limited to patients with systemic reactions to hymenoptera stings, who rarely have increased baseline serum tryptase, or in patients with unexplained episodes of anaphylaxis [127]. In these patients, bone marrow biopsy detects monoclonal mast cells that carry the mutant *KIT* D816V also detectable in bone marrow aspirate [128], and/or aberrant expression of CD2 or CD25. However, criteria for diagnosis of SM are not fulfilled, as only one or two minor criteria are met [104].

In conclusion, while symptoms due to release of mast cell mediators are present in most of the primary mast cell disorders, they also differ considerably: (a) Multifocal bone marrow mast cell aggregates and possible UP are only found in patients with SM; (b) D816V *KIT* mutation and aberrant CD25 expression on bone marrow mast cells characterizes patients with SM and monoclonal mast cell activation disorder (MMAD); (c) elevated baseline tryptase, and elevated baseline 24-h urine methylhistamine or PGD_2/11β-$PGF_{2\alpha}$ is found in most affected patients; (d) The response to anti-mediator therapy is variable and likely ineffective in patients with idiopathic anaphylaxis (IA) [99].

3.2. Reactive mast cell disorders

In these patients, no mutation of KIT D816V is found and flow cytometry is often negative for the expression of CD25 [98].

3.2.1. IgE-mediated hypersensitivity reactions—These are typical reactions (e.g. food, insect), due to aggregation of high-affinity IgE receptors (FcεRI) by allergen-bound IgE as was discussed earlier.

3.2.2. Drug-induced—Mast cells can respond to numerous drugs such as muscle relaxants, nonsteroidal anti-inflammatory, opioids, taxanes, and vancomycin. Such drugs can stimulate mast cells either directly or indirectly through G-coupled receptors [129]. It was recently discovered that the MRGPRX2 receptor is responsible for pseudo-anaphylactic reactions to many cationic drugs [30].

3.2.3. Mast cell hyperplasia—Hyperplasia in this context may be defined as increased disseminated mast cell density. This subvariant includes different diseases such as chronic infections, neoplasia, and autoimmune conditions that can stimulate mast cells through different mechanisms [98]. For instance, psoriasis is characterized by aberrant IFN-γ, which triggers mast cells through upregulation of high-affinity IgG receptors [130]. Mast cells in patients with rheumatoid arthritis are stimulated via C3a and C5a by binding to their respective receptors [130]. In patients with infectious diseases, mast cells are stimulated through the direct activation of Toll-like receptors (TLR) [131] that recognize molecular patterns common to microbial or viral pathogens.

However, there have been a number of reports of increased number of mast cells in the intestine of patients with SM [132], but also in the absence of SM in which case they may be termed ‘intestinal mastocytosis’ [133].

4. Mast cell mediator disorders

4.1. Clonal mast cell proliferation disorders

Most of these patients could have symptoms consistent with release of mast cell mediators.

4.2. Non-clonal mast cell mediator disorders

Most patients fall under this category that has also been called non-clonal mast cell activation disorder (nc-MCAS), mast cell activation syndrome (MCAS), or idiopathic MCAS[127] (Figure 2) depending on whether specific criteria are fulfilled [99,134–136]:

The second criterion listed above was recently modified [137,138] by excluding neurological symptoms, and emphasizing serum tryptase levels invariably leading to two subclasses of such patients, with or without serum tryptase elevations. In contrast, the symptom surveys of the mastocytosis society noted that >90% of patients reported ‘brain fog’ [139] as their major complaint and ‘stress’ as a key trigger [140,141]. Neuropsychiatric symptoms have been reported on many occasions [142–145]. Moreover, patients with mast cell disorders are profoundly affected by emotional stress via CRH [21,33,38,43]. In one case, UP expanded dramatically after emotional stress [146], while in another bone marrow mast cells were

shown to express CRHR-1 [147]. In addition to the potential triggers already discussed, one should include the effects of mold and mycotoxins in neuropsychiatric diseases [148,149]. For instance, yeast stimulates mast cells to secrete IL-6 and TNF without degranulation [150] and so does Borrelia burgdoferi spirochetes [151].

The disorders in this subcategory have no identifiable causes, no allergen-specific IgE and no detectable clonal mast cells, based on D816V *KIT* mutation. Environmental or endogenous stimuli, intrinsic mast cell defects may be involved. The best way to describe the status of the mast cells is that they are 'unstable,' exhibiting aberrant stimulation [152]. This 'unstable' status of mast cells may be affected by positive and negative signals [153], lower stimulation threshold, or even 'normal' secretion of mast cell mediators, but with an abnormal response of the surrounding tissues (e.g. deficiency of catabolic enzymes such as diamine oxidase and histamine N-methyltransferase). Moreover, unstable mast cells may retain a 'metabolic memory' of past triggers that prime mast cells to respond more rapidly and more severely to exposure of the same or different triggers even though the original trigger may no longer be present. One such example would be the ability of stress via CRH to prime mast cells for the action of IgE [51] or NT [23].

Diseases such as carcinoid syndrome, pheochromocytoma, gastrinoma, and VIPoma, which could explain many of the symptoms have to be ruled out through specific diagnostic tests. For instance, serum chromogranin A is a biomarker for carcinoid syndrome, but not for SM [154]. If mast cell clonality is absent, mast cell mediators (e.g. serum tryptase, and 24-h urine N-methylhistamine, PGD_2, $11\beta\text{-}PGF_{2\alpha}$) are measured in symptomatic patients (Figure 1). If these are not elevated, further clinical evaluation is necessary [118]. Idiopathic MCAS may be an underlying cause of various other frequent clinical presentations, like in subsets of patients with ME/CFS [81], fibromyalgia syndrome [82], and IBS [155,156].

'Activation' is usually inferred by release of mast cell mediators [157], primarily focusing on increased serum tryptase levels. However, serum tryptase levels could be both inadequate and misleading as mast cells can secrete many mediators especially cytokines and chemokines without any tryptase [31,60,61]. Tryptase is a key specific mediator for mast cells and it is recommended as the marker of choice, even though it is also released in small quantities by basophils [158,159]. Serum tryptase is usually detected with the B12 monoclonal antibody (mAb), which binds both alpha and beta tryptase. The G5mAb is bound with 10× more affinity to beta tryptase, so the alpha one is calculated as the difference between total and beta tryptase. The minimal increase in serum tryptase required as indicative of mast cell activation has been reported to be defined from the following equation: 20% of baseline tryptase level + 2 ng/ml + the baseline tryptase level = the value above which the definition of mast cell activation is met [98], usually ≥ 20 ng/ml. However, the sensitivity of this algorithm decreases with increased interval between resolution of symptoms and blood-draw [138]; moreover, there is no published data supporting this equation as has been extensively discussed in the past [160].

In addition, tryptase measurement could be affected by several conditions leading to false positive results: (a) presence of rheumatoid factor, (b) measurement of serum tryptase within 0.2–4 h after appearance of symptoms [98] if a symptomatic baseline level of serum tryptase

is available, then a rapid increase is considered a reliable index; (c) the baseline has to be assessed after the patient's complete recovery or during a symptom-free interval at least 24–48 h after complete resolution of all symptoms [161–163]; and (d) the sensitivity of tryptase algorithm decreases with decreasing clinical severity [138].

Histamine is specific for mast cells, but serum levels are not useful because histamine is metabolized very quickly (<1 min). Moreover, serum levels may be increased due to (a) release from basophils [158,159]; (b) tissue injury; (c) venous stasis, hemolysis or clotting during blood collection and sample preparation, or improper centrifugation/storage; (d) a diet rich in histamine [164]. The most informative test is measurement of the metabolite N-methylhistamine (30% of histamine) or 1-methyl imidazole acetic acid, MIA (60% of histamine) in 24 h urine or first morning urine collection, but must be kept cold during collection and sent to the laboratory cold; moreover, the patient should avoid consumption of foods containing biogenic amines (e.g. bananas, cheeses, spinach, sour crow, cumin, and other spices for 24 h before blood draw).

Serum PGD_2 may be useful, but its release can come from (a) cellular elements through processing of peripheral blood samples; (b) due to a diet rich in niacin or niacin products used to treat atherosclerosis [165]; and (c) there are no established criteria for its normal serum levels. Moreover, PGD2 is rapidly metabolized in blood and it should best be detected by measuring its metabolite 11β-$PGF_{2\alpha}$as was discussed earlier. One paper reported that out of 25 patients studied with MCAS, 24 urine 11β-$PGF_{2\alpha}$ was elevated in most and best correlated with flushing and itching [166].

Heparin is a specific mast cell mediator, and its increase in serum of SM patients has been documented [167].

In the absence of any inflammatory disease, serum IL-6 has been shown to correlate with disease severity and prognosis in SM [168–170]. A recent paper reported that increased serum levels of CCL2 strongly correlated with aggressive SM [171]. We recently reported impressive secretion of IL-31 from cultured human mast cells stimulated by IL-33 with or without SP or IgE [44]. Increased levels of SP were reported in the serum of SM patients [172].

4.3. Idiopathic anaphylaxis

These patients are characterized by (a) life-threatening anaphylactic reactions; (b) increased baseline levels of tryptase between the episodes; (c) absent mast cell clonality; and (d) acute onset of the disease. Anaphylaxis may be different in patients with IA (urticaria is present and serum IgE is significantly elevated) and patients with indolent SM (urticaria is absent during anaphylactic episodes and serum tryptase levels are significantly elevated) [112]. Recent evidence indicates that dendritic cells may deliver allergens to mast cells in the skin via extracellular microvesicles (exosomes) [173]. Evidently, mast cells can also secrete extracellular microvesicles [174] that may be directed specifically to T cells [175].

5. Histamine sensitivity

One must also consider patients who are either sensitive to histamine or have mutations in the gene diamine oxidase rendering them unable to metabolize histamine.

6. Activation threshold

There can be many reasons why mast cells can be stimulated to release their mediators (Table 8). Combination of triggers is more important than individual ones as they can lower the stimulation threshold of mast cells and 'prime' them for additional triggers [176] (Table 8). There are numerous examples of synergistic effects of different triggers. We reported that combination of CRH and NT have synergistic action in stimulating VEGF secretion without tryptase [23], as well as induce the expression of each other's receptors on human cultured mast cells [177]. We also showed that NT [177] and SP [178] increase expression of CRHR-1 on human mast cells. Moreover, SP increases expression of the IL-33 receptor ST2 and IL-33 increases NK-1 receptor on human mast cells [60]. Stimulation of mast cells by SCF also cross-activates ST2 [179].

7. Comorbidities

Symptoms alone and response or lack thereof to medication is not sufficient for diagnosis as many of the symptoms could derive from other pathologic entities, whether they implicate mast cells or not. Nevertheless, the presence of multisystemic manifestations of symptoms at the same time and in the absence of any other systemic disease is highly suspicious for the presence of some mast cell disorder. Symptoms suggestive of mast cell disorders that could be due to other conditions include: (a) 'flushing' is associated also with menopause, carcinoid syndrome, pheochromocytoma, medullary carcinoma of the thyroid gland, as well as ingestion of niacin; (b) cardiovascular disturbances may be related to myocardial infarction, endocarditis, autonomic dysfunction (dysautonomia), and postural orthostatic tachycardia syndrome (POTS), (c) gastrointestinal problems may implicate irritable bowel syndrome (IBS), food toxicity especially from spoiled scombroid fish (e.g. tuna) that generates large amounts of histamine, or neuroendocrine tumors such as VIPoma; (d) neurologic symptoms may be associated with panic attacks, migraines, epilepsy, and central nervous system (CNS) tumors; (e) respiratory signs may be part of asthma, 'heartburn,' angioedema; and (f) skin symptoms may be associated with acute toxic dermatoses, psoriasis, high parathyroid hormone (PTH), pemphigus vulgaris, and systemic lupus erythematosus (SLE). Other comorbid diseases include coronary hypersensitivity [180,181], and multiple chemical sensitivity syndrome (Table 1) [182]. Two particularly relevant diseases are Myalgic Encephalomyelitits/Chronic Fatigue Syndrome (ME/CFS) and ASD [81], both of which have recently been associated with focal inflammation of the brain [183].

We had reported that children with mastocytosis have a 10-fold higher risk of developing ASD [184]. ASD is a pervasive neurodevelopmental disorder characterized by deficits in communication, as well as the presence of restricted, repetitive behaviors [185–187]. Allergic symptoms, due to mediators secreted from mast cells, have been significantly

correlated with ASD severity [183,188]. A recent paper reported that diffuse cutaneous mastocytosis with the novel somatic *KIT* mutation K509I was associated with tuberous sclerosis, most of the may affected patient of which have ASD [189]. Large epidemiological studies have reported that allergies and asthma in preschoolers are significantly associated with ASD [190–193]. A similar conclusion was reached in a systematic review showing a significant association between atopic dermatitis and ASD [194]. Moreover, the presence of allergic symptoms strongly correlated with the presence of serum autoantibodies against brain peptides [195,196] in children with ASD [197].

Inflammation is a complicated immune process that involves numerous components depending on the tissue and trigger [198]. The specific role of cytokines in inflammation of the brain is still poorly understood as these ‘danger signals’ [45] are now divided into three different groups: (a) inflammatory cytokines, (b) alarmins, and (c) stressorins, with distinct patterns of secretion and biological properties [199]. Innate immunity of the brain involves primarily microglia [200], which communicate with mast cells [201,202]. Mast cell-derived mediators, such as histamine and tryptase, can activate microglia [203] leading to secretion of pro-inflammatory mediators including interleukins IL-1β, IL-6, and TNF, known to be increased in the brain of children with ASD [204]. Mast cells are found in the brain [205], especially the hypothalamus, thalamus, and third ventricle [206,207]. Mast cells are also found in the pineal, the pituitary, and the thyroid glands [3].

Mast cells can function as the ‘immune gate to the brain’ [208] as they can regulate permeability of the blood–brain barrier (BBB) [209–211] and are involved in neuroinflammation and brain disorders [76,212].

Therefore, a detailed medical history including type, duration and triggers of symptoms, careful and focused physical examination, and specific laboratory tests, is necessary for a proper clinical evaluation. Family history is of great importance because the prevalence of MCD is higher among relatives of MCD patients than would be expected by chance [213].

8. Treatment approaches

8.1. Disclaimer: although treatments are discussed, no endorsement or statement of safety is implied.

Unfortunately, the genetic cause of proliferative mast cell disorders and the effects of the multiple mediators released are reasons for the lack of curative treatments [214–216]. Limiting exposure to triggers, and reduction of symptoms is the main aim of treatment. Inhibiting secretion of mediators, especially cytokines, would be desirable [39],

Common triggers include alcohol, preservatives, spices, heat, cold, drugs [antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, neuromuscular junction blocking agent], radiocontrast media, hymenoptera stings, physical stimuli (pressure, friction), estrogen, and stressful conditions [113]. Reactions to hymenoptera may be the manifestation of nc-MCAD [217], and these patients should carry diphenhydramine (Benadryl, preferably liquid gels) and self-administered intramuscular epinephrine (EpiPen or AnaPen). Patients are usually administrated antihistamines, montelukast, and cromolyn (Table 9).

8.2. Antihistamines

Prevention of mast cell proliferation and secretion of mast cell mediators is the ultimate goal. Patients are typically treated with histamine (H_1,H_2)-receptor antagonists (antihistamines) (Table 9). Second generation antihistamines are preferred (loratadine, cetirizine, fexofenadine) because of less sedation and absence of any effects on cardiac excitation [218]. However, before or during invasive procedures (e.g. radiology studies), the first generation diphenhydramine or hydroxyzine would be best. Ketotifen, an H_1-receptor antagonist, is also a weak ocular mast cell inhibitor and may be used as a third option [219]. A number of patients who present with eosinophilic esophagitis or gastroenteritis are best treated with rupatadine, which also has anti-platelet activating factor (PAF) and anti-eosinophilic properties actions [220]; rupatadine can also inhibit cultured mast cells [220,221]. The H_2-antihistamines (ranitidine, famotidine) are used to block gastric hypersecretion [117]. However, histamine-1 receptor antagonists also have anticholinergic effects [222], and excessive doses may be associated with urinary retention [223] and negatively affect mental status [224,225].

8.3. Mast cell inhibitors

Despite the common use of the term ‘mast cell stabilizers’ [226], there are no such clinically effective drugs. Disodium cromoglycate (cromolyn sodium), known as a ‘mast cell stabilizer,’ reduces mostly GI symptoms, such as abdominal bloating and pain. Cromolyn is administered orally and is divided into doses [117]. Cromolyn causes tachyphylaxis [227], making it necessary to increase the dose from 100 mg tid to 400 mg tid over the course of a year. However, cromolyn is difficult to dissolve, less than 5% is absorbed orally and can cause severe diarrhea in about 15% of patients. Cromolyn can also cause alopecia in about 10% of patients. Recent data have even cast some doubt on the ability of cromolyn to stabilize human mast cells [228], and its beneficial effect on pruritus might be mediated by inhibition of C-fiber peripheral sensory nerves, instead [229].

8.4. Leukotriene receptor antagonists

Increased secretion of leukotriene E_4 has been reported in mastocytosis [230]. The cysteinyl-leukotriene receptor antagonist montelukast may be used in patients with refractory symptoms, especially patients with pulmonary involvement (asthma, wheezing).

8.5. Acetylsalicylic acid

Some patients with refractory flushing and elevated urinary 11β-PGF_{2a} have overproduction of prostaglandins [230]. These patients may benefit from acetylsalicylic acid (ASA) for clinical improvement [117,231,232]. However, others may experience hypersensitivity reactions and require desensitization treatment [230,233].

8.6. Omalizumab

Whether patients have elevated serum IgE or not, they may derive significant benefit from frequent use of omalizumab, an anti-IgE humanized murine mAb, approved for allergic asthma, and chronic urticaria. Omalizumab also improves patients in whom IgE levels are not pathologically increased [234]. Omalizumab, reversibly binds to the Fc portion of the

free serum IgE molecules, forming circulating immune complexes and reducing IgE binding to FcεRI on mast cells and basophils. As a consequence, FcεRI expression is down-regulated and, surprisingly, reactivity of these cells to other triggers (e.g. pressure) is also reduced [235]. A newer version of omalizumab, mepolizumab, may be equally suitable.

However, omalizumab can also form complement-fixing immune complexes that may lead to serious hypersensitivity reactions including severe 'serum sickness-like' reactions and should be administrated in a clinic under supervision. Both the US FDA and the EU EMA have directed inclusion of these potential serious adverse effects in the specialized information accompanying this drug.

Given that omalizumab targets components of the immune system, it may potentially increase the risk of infections or neoplasms.

8.7. Corticosteroids

Corticosteroids could be of great benefit in patients with refractory symptoms especially after resuscitation from an acute episode of anaphylaxis along with the use of subcutaneous epinephrine (EpiPen), and β-agonists [117]. However, there are reported instances of sensitivity to steroids, and their prolonged use is associated with asteoporosis, and depression.

8.8. Venom immunotherapy

Treatment with lifelong venom immunotherapy (VIT) is necessary for patients with MMCAS after hymenoptera stings, especially if they test positive for venom specific IgE [236]. This treatment could have life-threatening side effects and should be undertaken with caution in a clinic under supervision after weighing the risk-benefit for the individual patient.

8.9. Immune Ig

In certain cases, where all else has failed, patients may be treated with immune Ig (ivIg).

8.10. Specific agents

Patients with advanced SM without the D816V *KIT* mutation may be treated with the tyrosine kinase inhibitor (TKI), imatinib. Another TKI, dasatinib, inhibits D816V KIT expressing mast cells *in vitro*, but has not been proved successful in clinical trials. A protein kinase C (PKC) inhibitor (previously known as PKC412) approved recently, midostaurin, can inhibit mast cells expressing D816V *KIT* and was recently approved for advanced forms of clonal proliferative mast cell disorders such as aggressive SM and mast cell leukemia [237]. However, PKC is an important enzyme present in most cells, not only mast cells; hence, the benefit–risk assessment must be carefully weighed. An experimental TKI, avapritinib (formerly known as BLU-285) appears to have even greater ability to reduce mutated KIT mast cells [238].

8.11. Flavonoids

Flavonoids such as quercetin (3′, 4′, 5, 7, 9-pentahydroxyflavone) and luteolin (3′, 4′, 5, 7-tetrahydroxyflavone-NOT lutein, which is a carotenoid) are naturally occurring polyphenolic compounds with potent anti-oxidant, anti-inflammatory, and neuroprotective actions acting by inhibiting multiple targets [239–241]. It was previously shown that flavonols containing more hydroxyl groups have greater anti-oxidant and anti-inflammatory activity [19,209,242], as well as anti-asthmatic effects [218].

8.11.1. Luteolin—Luteolin inhibited mast cells [76,243–245] and decreased histamine secretion in bronchoalveolar lavage fluid from conscious ovalbumin sensitized guinea pigs exposed to aerolized ovalbumin [246]. Luteolin-7-O-glucoside inhibited degranulation and leukotriene production from bone marrow mast cells [247]. Luteolin also inhibited stimulation of human T cells [78], keratinocytes [248], and astrocytes [249]. Luteolin inhibited microglial activation and proliferation [250–254]. A luteolin containing formulation was recently shown to have significant benefit in children with ASD [242,255].

Luteolin also has neuroprotective actions [256–258] and protected against thimerosal-induced inflammatory mediator secretion from human mast cells [244] as well as from methylmercury-induced mitochondrial damage [259]. Luteolin induced synthesis and secretion of neurotrophic factors including nerve growth factor (NGF), Glia-derived growth factor (GDGF), and brain-derived neurotrophic factor (BDNF) [260]. Luteolin is structurally related to 7,8-dihydroflavone, which was shown to have BDNF activity [261], and reduce symptoms in a mouse model of Rett syndrome, most patients with which have symptoms of ASD [262]. Moreover, 3′,4′-dimethoxyflavone was shown to be protective against parthanatos [263].

Both luteolin and tetramethoxyluteolin blocked stimulated intracellular calcium increase [245] and activation of NF-κB in human leukemic HMC-1 mast cells [264]. Moreover, polyphenols have been reported to inhibit mast cell secretion by interfering with the secretory vesicle fusion [265]. The substitution of luteolin's four hydroxy groups by methoxy groups apparently enhances its anti-inflammatory activity and its benefit in neurodegenerative diseases [266–268].

Flavonoids are difficult to absorb (<10%) after oral administration [269,270] and are extensively metabolized [270–272]. We have been investigating the luteolin structural analog 3′,4′,5,7-tetramethoxyflavone (tetramethoxyluteolin), it is a more potent inhibitor than luteolin on human cultured microglia [251] and mast cells [76]. Methylation of dietary flavones greatly improved metabolic stability and intestinal absorption [273].

Flavonoids are generally considered safe [274–277], and can even protect against chemically induced liver toxicity, a common consequence of many drugs [278]. Moreover, neither luteolin nor tetramethoxyluteolin affects viability of cultured human mast cells [245], T cells [78] or keratinocytes [279]. Luteolin also improved symptoms of ASD [242,280], post-Lyme syndrome [281], and brain fog [139] without any major adverse effects.

However, there should be caution against using flavonoid preparations of unknown source and purity because the cheapest sources are peanut cells and fava beans that could lead to anaphylaxis or hemolytic anemia in G_6PD individuals, respectively.

Treatment with luteolin should best be used together with a tetramethoxyluteolin containing skin lotion [282], and requires a few weeks before mast cells are sufficiently inhibited. Luteolin may also be combined with vitamin D3, which has been reported to have anti-allergic actions [283].

9. Summary

A possible treatment approach of patients with mast cell mediator release disorders would be as follows (Table 9): (1) Antihistamines (cetirizine, diphenhydramine, hydroxyzine); (2) antihistamines with anti-eosinophilic action (ketotifen, rupatadine); (3) antihistamine with antiserotonin action (cyproheptadine); (4) tricyclic antidepressants with combined antihistamine action (doxepin); (5) flavonoids (luteolin, quercetin of high purity and increased absorption); (6) antileukotrienes (montelukast); (7) cromolyn sodium; (8) steroids (methylprednisolone); (9) epinephrine (EpiPen, AnaPen); (10) anti-IgE (omalizumab), kinase inhibitors (imatinib, mitostaurine, avapritinib) should be reserved for aggressive SM or mast cell leukemia.

Bone pain is quite common in patients with mast cell disorders and should be addressed [160,216]. Unlike morphine, which is a strong trigger of mast cells, the synthetic opioids tramadol and piritramide (not available in the US) seem to be tolerated. Ketamine and/r propofol, alone or with loaratadine, could be used for anesthesia. Some patients could also tolerate transdermal fentanyl. Low-dose naltrexone, an opioid receptor antagonist, may also be helpful.

Patients with migraine headaches could be helped prophylactically with cyproheptadine or with prochlorperazine, both of which also inhibit human mast cells [284].

10. Expert opinion

Recent reviews stress the role of mast cells in health [285] and disease [215,286], especially their responsiveness to non-allergic triggers [286,287]. There has been considerable progress in defining *KIT* mutations and developing drugs that block tyrosine kinases (TK) that are involved in mast cell proliferation [288]. However, it has become clear that *KIT* mutations alone are not able to induce a mast cell proliferative disorder; as a result, the aim of recent research for therapeutic agents is the development of multitargeting drugs. Moreover, our understanding of mast cell stimulation by non-IgE mediated triggers remains poor, and there are still no clinically effective inhibitors of mast cell mediator release. One of the possible reasons for this problem has been the over-reliance on use of rodent mast cells, the results from which have increasingly been shown not to reflect human inflammatory diseases [289].

Moreover, both immortalized and primary normal mast cells cultured from peripheral blood or umbilical cord blood require 8–12 weeks of growth and are ‘immature’ with poorly developed secretory granules [60]. More importantly, mast cells from different tissues are

phenotypically very different [290]. For instance, brain mast cells do not express FcεRI [207], skin mast cells are triggered by morphine, while heart mast cells are not. Moreover, we still do not know differences in cytokine/chemokines release or other mediators. It would be desirable to identify mechanisms and mediators that may contribute to useful physiology as compared to pathological function, and thus stimulate them or inhibit the, respectively. For instance, mast cells have been reported to regulate wound healing in diabetes [291], but contribute to cancer growth and metastasis [292].

Finally, there is the mystery of the presence of mast cells in neuroendocrine organs, such as the pineal, hypothalamus, pituitary, thyroid, and the uterus [3], where the pathophysiologic function of the mast cells remains unknown. These findings may possibly explain our observation that many females with MCMD report increased libido and orgasms [3]. An intriguing relevant observation was the increase of number of mast cells in the habenula of female pigeons during courting [293], and the development of a female ‘phenotype’ in newborn female rats in which mast cells were stimulated [294].

Research efforts should focus on (a) establishing normal mast cell cultures that mimic those in different tissues; (b) investigating the ability of mast cells to respond to different triggers with selective release of mediators; (c) identifying the molecular events involved in mast cell release of inflammatory mediators; (d) studying the role of growth factors other than SCF, such as NGF and platelet-derived growth factor (PDGF); (e) investigating the synergistic actions of triggers, such as SP an IL-33; (f)determining the role of extracellular microvesicles [295]; (g) as well as identifying any innate inhibitors such as the polyamines agmantine (the product of the decarboxylation of arginine) [296] or spermidine and spermine (the products of the decarboxylation of ornithine) [297,298], as well as heparin and chondroitin sulfate [299].

One paper reported on a prototype inhibitory receptor (mast cell functional-associated antigen, MAFA), which selectively regulates FcεRI-stimulated mast cell secretion of IL-1β and CXCL8, but not TNF or MCP-1 [300], but there has not been any apparent further development.

There has been recent interest in the potential mast cell inhibitory ability of the anti-inflammatory cytokine IL-37 [301–303], at least in diseases where mast cells have been implicated [303,304], but direct inhibition of human mast cells has not been reported so far.

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Article highlights

- The term MCMD should be used when specific criteria.
- Tryptase is specific for mast cells and is used for diagnosis, but is often not secreted and its function is still not known. Measurement of other serum mast cell mediators, especially IL-6 and IL-31, as well as CCL2 and CXCL8, and urine (24 h) histamine metabolites (methyl histamine, MIA), the PGD_2 metabolite (11β-$PGF_{2\alpha}$), and LTE_4 should be considered in the absence of any other inflammatory conditions.
- Screening tissue sections for mast cells should combine immunohistochemistry for CD117 (identifies all mast cells) and tryptase (identifies degranulated mast cells).
- Single cell laser microcapture and qRT-PCR should be used to identify mast cell phenotype variability and mediator synthesis/release *in situ*.
- Special attention should be placed on the timing of measurement of mast cell mediators and patient symptoms as mast cells have been shown to be regulated by a circadian clock.
- There is no curative treatment for MCMDs at the present time. Prevention of stimulation of mast cells and reduction of the effects of their mediators are necessary. Step-wise increase in treatment is recommended as indicated and tolerated.

Development of effective mast cell inhibitors should be a top priority. Recent promising results from the use of tetramethoxyluteolin and IL-37 should be expanded in appropriate formulations.

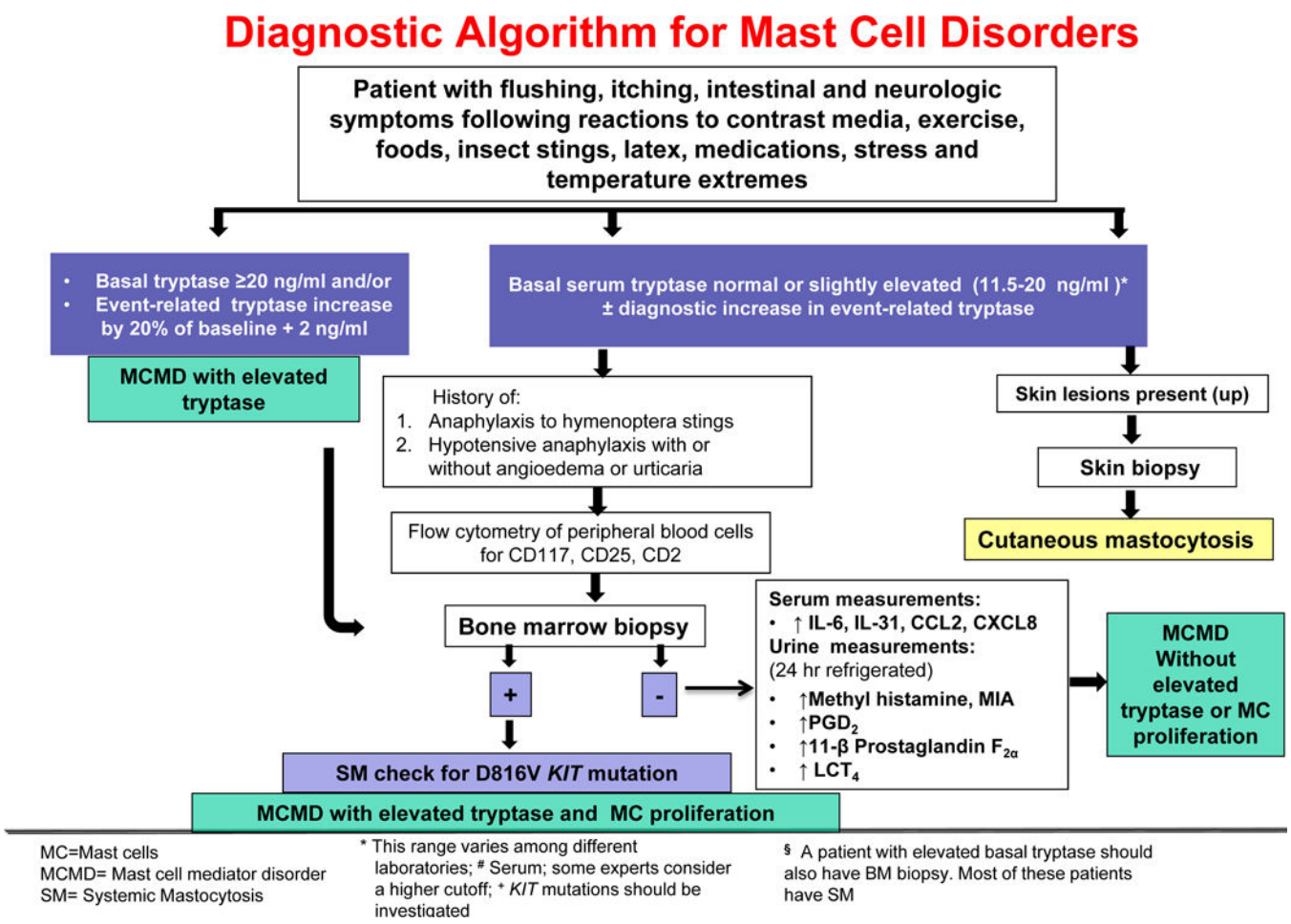

Figure 1.

Diagrammatic representation of a proposed diagnostic rubric for mast cell mediator disorders with emphasis on clonal and non-clonal subtypes, and the presence or absence of elevated serum tryptase.

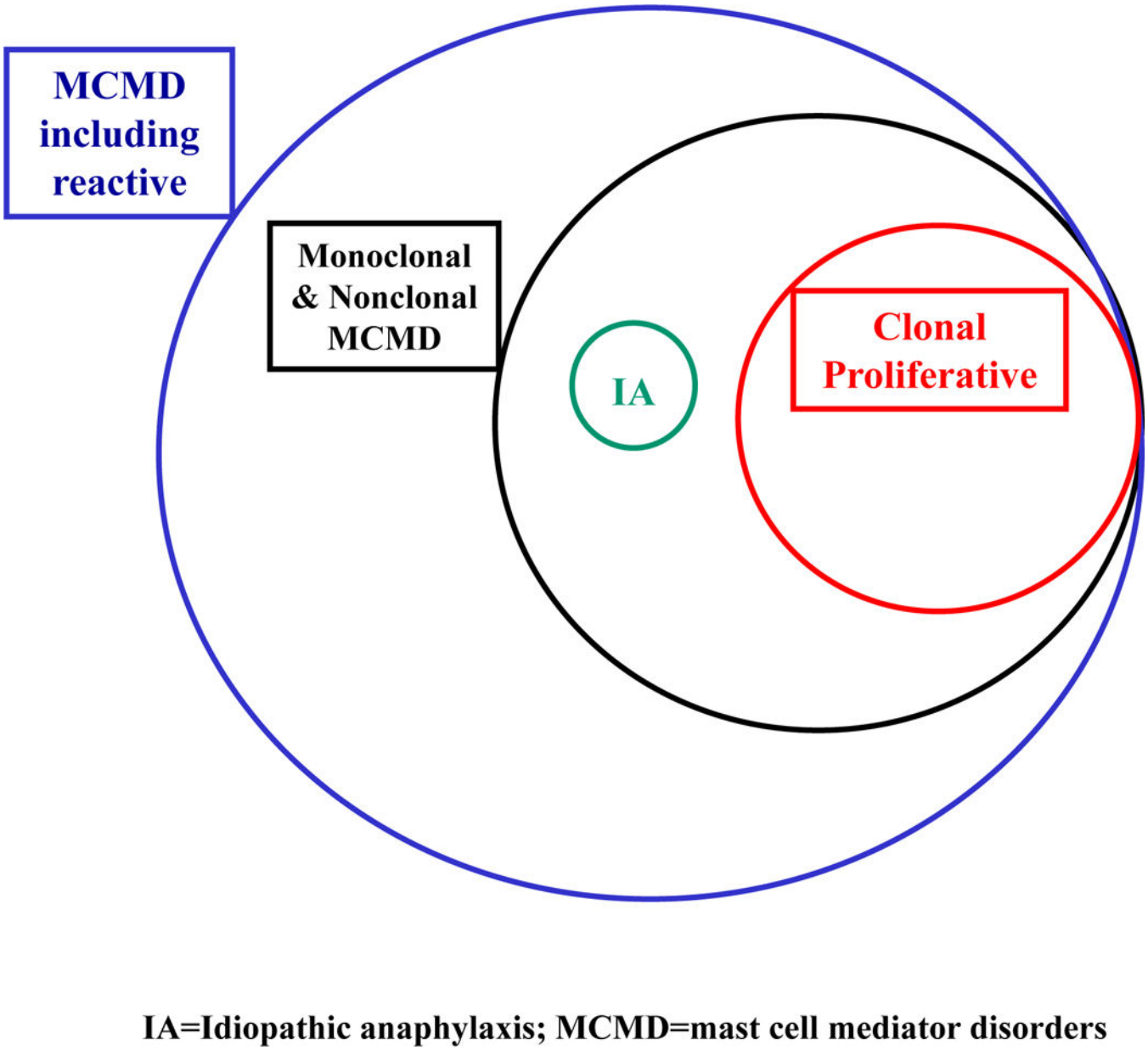

Figure 2.

Estimated occurrence and overlapping nature of mast cell mediator disorders with respect to clonal and non-clonal subtypes: (a) clinical signs and symptoms; (b) documentation of increased serum and/or 24 h urine mast cell mediators or their metabolites; and (c) reduction in symptoms following treatment with drugs that inhibit stimulation of mast cells or the action of their mediators.

Table 1.

Common Symptoms in Patients With Mast Cell Mediator Disorders

• Cardiovascular: chest pain, hypotension, hypotensive syncope, tachycardia
• Dermatologic: angioedema, dermatographism, flushing, pruritus, urticaria pigmentosa
• Gastrointestinal: abdominal crumping/pain, bloating, diarrhea, esophagitis, nausea, vomiting
• Musculoskeletal: bone/muscle pain, degenerative disc disease, osteoporosis/osteopenia
• Naso-ocular: nasal congestion, pruritus, tearing
• Neurologic: headache, memory and concentration difficulties (brain fog), paresthesias, peripheral neuropathy
• Respiratory: hoarseness, sore throat, stridor, throat swelling, wheezing
• Systemic: anaphylaxis, fatigue

Table 2.

Conditions Often Comorbid With Mast Cell Diseases

• Chronic inflammatory response syndrome (CIRS)
• Fibromyalgia syndrome (FMS)
• Ehlers-Danlos Syndrome (EDS)
• Gulf War Illness (GWI)
• Interstitial cystitis/bladder pain syndrome (IC/BPS)
• Irritable bowel syndrome (IBS)
• Kounis syndrome
• Multiple chemical sensitivity syndrome (MCSS)
• Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
• Post-Lyme syndrome
• Postural orthostatic tachycardia syndrome (POTS)
• Post-traumatic stress disorder (PTSD)

Table 3.

Cell Triggers of Mast Cell Degranulation

Acetylcholine
Complement fragments
- C3α, C4α, C5α
Drugs
- Local anesthetics
- Lactam antibiotics
- Neuromuscular junction blockers
- Vancomycin
IgE
IgG_1
IgG_4
Lysophosphatidylserine
Peptides
- Adrenomedullin
- CGRP
- Endorphin
- Endothelin
- Eosinophil granule proteins
- Hemokinin-1
- Leptin
- Mastoparan
- Neurotensin
- NGF
- PTH
- Somatostatin
- SP
- Thrombin
- VIP
Physical conditions
- Cold
- Heat
- Pressure
- Stress
- Vibration

Table 4.

Triggers of Mast Cells Without Degranulation

Triggers	Mediator
Peptides	
CRH	VEGF
SCF	IL-6
Cytokines	
IL-1β	IL-6
IL-33	IL-31
IL-33	CX CL8 (IL-8)
IL-33 + SP	TNF, VEGF
Heavy metals	
Aluminum	
Cadmium	
Mercury	
Herbicides	
Atrazine	
Glyphosate	
Pathogens	
Borrelia (Lyme disease) *	TNF
LPS	TNF
Poly (I:C) (viruses)	IL-6, TNF
Sporothrix (mold) *	IL-6, TNF

* Mycotoxins

Table 5.

Mast Cell Mediators

Prestored
Biogenic Amines
Dopamine
Histamine
5-Hydroxytryptamine (5-HT, serotonin)
Polyamines
Spermidine, spermine
Cytokines
TNF
Enzymes
Arylsulfatases A
Beta-hexosaminidase
Beta-glucuronidase
Beta-glucosaminidase
Beta-D-galactosidase
Carboxypeptidase A
Cathepsins B,C, D, E, L
Chymase
Garnzyme B
Kinogenases
Phospholipases
Renin
Tryptase
Metalloproteinases
(CPA3, MMP9, ADAMTSS)
Growth factors
FGF
NGF
SC
TGFβ
VEGF
Peptides
ACTH
Angiogenin
Angiopoietin
Calcitonin gene-related peptide
Corticotropin-releasing hormone
Endorphins
Endothelin
Hemokinin-1

Kinins (bradykinin)

Leptin

Melatonin

Neurotensin

RANKL

Somatostatin

Substance P

Urocortin

Vasoactive intestinal peptide

Proteoglycans

Chondroitin sulfate

Heparan sulfate

Heparin

Hyaluronic acid

Serglin

De novo synthesized

Chemokines

IL-8 (CXCL8), MCP-1 (CCL2), MCP-3 (CCL7),

MCP-4, RANTES (CCL5), Eotaxin (CCL11)

Cytokines

IL-1β, IL-4, IL-5, IL-6, IL-15, IL-17, IL-31, IL-33, TNF

Growth Factors

SCF, β-FGF, neurotrophin 3, NGF,

PDGF, TGFβ, VEGF

Nitric oxide

Phospholipid metabolites

Leukotriene B_4

Leukotriene C_4

Platelet activating factor

Prostaglandin D_2

Table 6.

Classification of Mast Cell Disorders

Clonal Mast Cell Proliferation Disorders
1. Systemic mastocytosis (indolent, aggressive)
2. Cutaneous mastocytosis (urticarial pigmentosa, diffuse, telangiectasia macularis eruptive persistans)
3. Mast cell leukemia (MCL)
4. Mast cell sarcoma (MCS)
5. Extracutaneous mastocytoma (benign)
6. Monoclonal mast cell activation syndrome (MMAS)
Mast Cell Mediator Disorders (Idiopathic)
1. Monoclonal without abnormal clustering
2. Non-clonal
3. Idiopathic anaphylaxis (IA)
Reactive Mast Cell Proliferation/Mediator Release Disorders
1. IgE-mediated hypersensitivity reactions (e.g. food, insect anaphylaxis)
2. Drug-induced (e.g. vancomycin, opioids, taxanes, muscle relaxants, adenosine, nonsteroidal anti-inflammatory)
3. Mast cell hyperplasia (related with chronic infections, neoplasia, autoimmune conditions due to a possible excess of stem cell factor)

Table 7.

Diagnostic Criteria for Systemic Mastocytosis

Major criterion	a. Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in intramedullary biopsy sections and/or extramedullary organ(s).
Minor criteria	a. In intramedullary biopsy sections or other extramedullary ones >25% of the mast cells in the infiltrate are spindle shaped or have atypical morphology, or of all mast cells in bone marrow aspirate smears >25% are immature or atypical
	b. Gain of function point mutation of KIT at codon 816 (usually KIT D816V) in bone marrow, blood, or other extracutaneous organ
	c. Aberrant immunophenotype of mast cells of CD_2 and/or CD_{25} in bone marrow, blood, or other extracutaneous organ (in addition to normal mast cell markers)
	d. Persistently elevated baseline serum total tryptase (>20 ng/ml).

Table 8.

Proposed Pathogenetic Mechanisms for Mast Cell Mediator Disorders

Lower activation threshold due to decreased expression/function of inhibitory molecules/pathways.
Intracellular
PTEN ↓
Chondroitin sulfate ↓
Sergylin ↓
Spermine/spermidine ↓
TGF beta ↓
Extracellular
Deflisinc ↓
IL-10 ↓
IL-37 ↓
IL-38 ↓
TGF beta ↓
Combination of non-allergic triggers
Peptides and Cytokines
SP + IL-33
NT + CRH
HK-1 + IL-33
Unappreciated triggers
CRH
Borrelia toxin
Bradykinin
CGRP
RCAP
Mycotoxins
NGF
Poly (lic)
PTH
Stress
Autocrine effects
Secretion of autocrine mediators
CRH
NK-1
Neurotensin
Tryptase
Autocrine receptor expression
Secretion of autocrine mediators
NT → CRHR-1 ↑
SP → CRHR-1 ↑
CRH → NTR ↑

SP → STZ ↑

IL-33 → NK-1 ↑

Table 9.

Treatment Approach for Mast Cell Mediator Disorders

1. Antihistamines (cetirizine, diphenhydramine, hydroxyzine)
2. Antihistamines with anti-eosinophilic action (ketotifen, rupatadine)
3. Antihistamine with antiserotonin action (cyproheptadine)
4. Tricyclic antidepressants with combined antihistamine action (doxepin)
5. Flavonoids (luteolin, quercetin of high purity and increased absorption)
6. Antileukotrienes (montelukast)
7. Cromolyn sodium
8. Steroids (methylprednisolone)
9. Epinephrine (EpiPen, AnaPen)
10. Anti-IgE (omalizumab)
11. TK inhibitor (imatinib)
12. Kinase inhibitors for mast cells expressing mutant *KIT* (mitostaurine, avapritinib)