Review

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Progress in mast cell activation syndrome: the global consensus-2 diagnostic criteria at six years

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Abstract: Since establishment in 2020 of the global consensus-2 diagnostic criteria for mast cell activation syndrome (MCAS), recognition of this prevalent disease, existing alongside rare cutaneous or systemic mastocytosis, has grown significantly. Despite this progress, some have continued using more restrictive criteria, significantly underdiagnosing this complex but treatable disorder. Consensus-2 has brought diagnosis and effective treatment in many MCAS patients previously labeled with unexplained (mostly inflammatory) syndromes or misdiagnosed as somatization or other primary psychiatric disorders. Fears that consensus-2 diagnostic criteria might bring overdiagnosis have not been realized. Appropriate therapy for MCAS can dramatically improve quality of life, sometimes after decades of morbidity and disability despite extensive past unhelpful workups and treatment. Appreciating the breadth and heterogeneity of MCAS, and achieving good management outcomes, requires understanding the complexity of mast cell biology and pathophysiology as well as the range of comorbidities the disease can drive and which can aggravate the disease. The spectrum of diseases thought possibly rooted in variants of MCAS (or to which MCAS is significantly contributing) continues expanding, calling for more research. New therapeutic options have emerged, and clinicians have gained better appreciation for use of existing treatments and mitigation of impediments to treatment. MCAS research remains in early stages, hampered by many factors including limited awareness of the disease and challenges in objective assessment of treatment response. This review examines developments in awareness, education, clinical care, and research since consensus-2 emerged, while discussing challenges and opportunities for accelerating progress.

Keywords: mast cell activation syndrome (MCAS); mast cell activation disease; mast cell disease; chronic illness; misdiagnosis; medical controversies

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Introduction

Dominantly at environmental interfaces and abutting all vessels and neurons, mast cells (MCs) contribute to innate and adaptive immunity and homeostasis [1–4]. With such sitings and responses magnitudes faster than other leukocytes, MCs are first-line sentinels against bodily assaults [5]. Long before emergence of other leukocytes, MCs comprised the entirety of the eukaryotic immune system [6], developing wide-ranging abilities to recognize and respond to threats. Though other leukocytes emerged to better handle specific threats and now

dominate modern immunity, MCs have persisted and still express hundreds of mediators and receptors, conferring remarkable capacities to recognize, and to facilitate resistance to and recovery from, vast arrays of insults [7, 8]. However, aberrancies in MC mediator expression [a.k.a. MC "activation" (MCA)] can leverage this diversity to compromise health in many ways. Emerging research is increasingly suggesting most MC disorders are rooted in (usually somatic) variants in assortments of MC regulatory genes [9, 10], always bringing some extent of aberrant MCA [i.e., one (yet undistinguished) type or another of "MC activation syndrome" (MCAS)]. Occasionally, KIT codon 816 variants are also present, usually conferring substantial MC neoplasia ("mastocytosis", common in some animals [11, 12] but rare in humans [13–17]) in addition to symptoms from the other variants (i.e., making MCAS "part and parcel" of mastocytosis). However, most MCAS patients do not meet diagnostic criteria for systemic or cutaneous mastocytosis and suffer symptoms stemming directly and/or indirectly from aberrant MC mediator expression, impacting cells, tissues,organs, and systems throughout the body with dominantly inflammatory, allergic, and dystrophic effects but sometimes also coagulation and endocrine disruptions and other issues [7].

Cutaneous and systemic mastocytosis have been recognized for approximately 150 and 100 years, respectively. In the 1980s, MCAS was first hypothesized to exist based on reasoning that if mastocytosis involves both substantial MC proliferation and chronic inappropriate MCA, then diseases of inappropriate MCA without substantial MC neoplasia likely also occur [18–21]. Two decades have passed since the first case reports of MCAS [22, 23].

Two schools of thought have emerged regarding the scope of MCAS, appropriate diagnostic criteria, and reasonable treatment approaches [24, 25]. One perspective, "consensus-1" [26–46], emerging from an earlier proposal [47] and labeled by its authors as "the consensus" or "the global consensus", has persistently expressed the sense that MCAS is rare (similar to mastocytosis) and usually idiopathic. Additionally, consensus-1 characterizes MCAS as typically involving recurrent anaphylaxis and rises in serum tryptase concentrations of at least 20% above baseline asymptomatic levels, plus an additional 2 ng/mL (rises so subtle that the higher level often is still within the normal range), and which must be found to occur within 4 h of symptom onset. Tryptase is a multifunction protease which MCs constitutively express and represents approximately 25 % of total MC protein content [48, 49]. Recent updates to consensus-1 criteria now allow alternative biomarkers for MCA when tryptase testing cannot be used or yields "unclear" results (though what is meant by "unclear" is unclear). Accepted alternatives are limited – urinary *N*-methylhistamine and 2,3-dinor-11β-prostaglandin-F2α (metabolites of histamine and prostaglandin D2 (PGD2), respectively) at least twice their baseline levels [36–39] – challenging criteria given significant hurdles in accurately determining their levels, especially at a truly asymptomatic baseline or so quickly (within 4h) soon after symptom onset.

An alternative perspective, now called "consensus-2" [25, 50] (Table 1), emerged almost simultaneously but regards MCAS as prevalent (approximately 17–20 % of the Western population) [15, 51] and commonly presenting with diverse manifestations stemming from diverse profiles of aberrant release of MC mediators with very diverse effects [52, 53]. Consensus-2 recognizes MCAS usually shows no significant tryptase elevation and uncommonly manifests anaphylaxis [53, 54]. Consensus-2 encourages measurement of other MC-specific mediators (see Table 1). Furthermore, consensus-1 advocates maintain no specific MC count in tissues can be considered abnormal unless the unique MC histomorphologic anomalies in mastocytosis are present [55–57], while consensus-2 considers MC counts exceeding 20 per high-power (400×) field in gastrointestinal and genitourinary tissues to be abnormal, even with histomorphologically normal MC appearance (as is typical in MCAS) [25, 58–60].

Analyses of these perspectives have been published [24, 25]. Though assertions of validity and superiority of consensus-1 have been published by its advocates [28, 39, 61, 62], actual evidence has been limited to select anaphylactic scenarios in small cohorts and have provided little data to support a restricted view of MCAS [63–69].

Consensus-2 has been criticized, too [27, 28, 39–42, 62]. One study claimed consensus-2 has low sensitivity for detecting MCAS, though it used diagnostic tests not typically employed by either consensus (KIT-D816V mutation analysis, flow cytometry, and marrow examination) [70]. Another study utilized artificial intelligence systems – some known for generating erroneous or fabricated findings – to conclude consensus-2 diagnoses were "more variable" and "less precise" than consensus-1 diagnoses [71], perhaps unsurprising when comparing restrictive vs. broader diagnostic criteria.

Meanwhile, evidence supporting consensus-2 has been growing [4, 51, 59, 60, 72–96]. This review details recent developments regarding diseases likely intersecting with MCAS, diagnostic and therapeutic issues in MCAS, and research issues in MCAS. Summaries of these developments are provided here; additional details are provided in the Supplementary Material, Appendix.

Table 1: Consensus-2 Diagnostic Criteria for mast cell activation syndrome.

Major criterion
1. Constellation of clinical complaints in two or more systems attributable to pathologically increased MC activity (MC mediator release syndrome)
Minor criteria
1. Multifocal or disseminated infiltrates of MCs in marrow and/or extracutaneous organ(s) (e.g., gastrointestinal or genitourinary tract; >19 MCs/high power field)
2. Abnormal spindle-shaped morphology in >25 % of MCs in marrow or other extracutaneous organ(s)
3. Abnormal MC expression of CD2 and/or CD25 (i.e., co-expression of CD117/CD25 or CD117/CD2)
4. MC genetic changes (e.g., activating KIT codon 419, 509 or 560 mutations) shown to increase MC activity
5. Evidence [typically from body fluids such as whole blood, serum, plasma, and/or urine (random and/or 24-h)] of above-normal levels of MC mediators including:
– Tryptase
– Histamine or its metabolites (e.g., N-methylhistamine)
– Heparin
– Chromogranin A (note potential confounders of cardiac or renal failure, neuroendocrine tumors, or recent proton pump inhibitor use)
– Other relatively MC-specific mediators (e.g., eicosanoids including prostaglandin (PG) D_2, its metabolite 11-β-$PGF_{2\alpha}$, or leukotriene E4)
6. Symptomatic response to inhibitors of MC activation or MC mediator production or action

Diagnosis established upon demonstration of the major criterion combined with at least one minor criterion (and in the unstated but inferred absence of any other disease better accounting for the patient's problems).

Diseases likely intersecting with MCAS

Given the diversity in mediator expression and distribution of MCs, a limited presentation scope for MCAS would be surprising. Instead, the overarching theme of MCAS's clinical presentation (chronic multisystem polymorbidity of generally inflammatory, allergic-type, and dystrophic issues) follows from the dominant effects of the mediators. With few symptoms being highly specific to MCA, it instead is the totality of "MCAS-consistent" presentation/behavior (and absence of better unifying diagnosis), preferably together with laboratory evidence, which allows confident diagnosis of MCAS. Beyond mere awareness of the existence of MCAS, this marked heterogeneity in MCAS's superficial clinical presentation challenges clinicians, impeding initial recognition that MCAS belongs in the differential diagnosis.

Such heterogeneity brings potential for MCAS to "be involved in" (including potentially being the root cause of) a wide range of "idiopathic" clinical phenomena/disorders/diseases. For example, there is growing evidence that MCAS often is involved in various inflammatory disorders and unusually severe acute and chronic courses of some infections, such as Covid-19 [84, 97, 98] or certain vector-borne infections [99]. MCs manifest innate and acquired/learned immunity, but the ability of dysfunctional MCs to learn which novel exposures are harmful may be impaired, and their responses may be exaggerated, to various chemical compounds of the modern era (including many medication product excipients (fillers, preservatives, dyes, etc.) and implanted foreign materials [80–82, 100–104]) for which innate tolerance has not yet evolved.

Neuronal abutment by MCs [105, 106] suggests mast cell involvement likely underlies (or significantly contributes to) many cases of a broad swath of idiopathic manifestations of central and peripheral nervous system disorders, including many categorized as "neurologic" (e.g., paresthesia, headache, tics, tremor), "cognitive" (e.g., autism, attention deficit and hyperactivity disorders, disorders of memory and word-finding often colloquially labeled as "brain fog"), "psychiatric" (especially anxiety and mood disorders), and "autonomic" (including dysregulation of temperature, heart and respiratory rates, blood pressure, gastrointestinal motility, sweating, sleep, etc.). [4, 74, 107]. Reactive anxiety and/or depression can develop from ineffective evaluation and treatment (or misattribution of symptoms to psychosomatism), and chronic neuroinflammation can cause significant neurologic dysfunction. However, much of the neurologic manifestations often seen in MCAS could be due to normal nerve fibers reacting to constant aberrant expression of heterogeneous potpourris of potent mediators from some (likely mutated, i.e., primarily dysfunctional) subpopulation of MCs.

The expansive repertoire of MC cell-surface receptors includes receptors for the major sex hormones [108]. Ligand binding to some (e.g., progesterone, testosterone) may inhibit MCA in some patients, while others (e.g., estrogen) almost always increase MCA (and further activate aberrant MCs in aberrant ways), leading to involvement of MCAS in many menstrual, fertility, and pregnancy disorders [91, 92]. MC expression of receptors and mediators relevant to other endocrine systems brings common involvement in other endocrinologic disorders, too.

Many MC mediators help guide growth/development in many tissues, creating potential for involvement of MCAS in many benign and malignant dystrophisms, potentially at any site. Features of MCA are commonly seen [109] in patients with some connective tissue disorders [e.g., hypermobile Ehlers-Danlos Syndrome (hEDS)] for which no causative germline mutation has yet been found, increasing suspicion that some connective tissue disorders may often be rooted in certain forms of (again, mostly somatically mutated) MCAS (or at least that MCAS is significantly contributing to the development of those disorders) [93, 110]. Recognition in some patients of certain recurrent patterns of comorbidities associated with (and perhaps rooted in) MCAS – such as a “pentad” including the chronic multisystem inflammation of MCAS plus connective tissue disorders, dysautonomia, gastrointestinal dysmotility, and autoimmunity – has been slowly increasing, too [77, 78, 111–113]. In addition to MCAS’s involvement in some vasospastic incidents (Kounis syndrome), MCAS may sometimes drive the dystrophisms underlying some vascular compression syndromes such as median arcuate ligament syndrome (MALS), nutcracker syndrome, and pelvic vein congestion syndrome [114–118].

More details regarding data and perspectives recently emerging regarding the wide array of long-idiopathic disorders in which MCAS of one variant or another might have a pivotal role (e.g., long-Covid syndrome, multiple chemical sensitivity (or, as more recently termed, toxicant-induced loss of tolerance (TILT)), dysautonomia, etc.) can be found in Section 1 of the Supplementary Material, Appendix.

Diagnostic issues in MCAS

In addition to differences between consensus-1 and consensus-2 regarding MCAS scope and diagnostic criteria, other diagnostic challenges have become evident.

The marked thermolability of most of the clinically measurable MC mediators fairly specific to the MC makes accurate testing challenging [24, 25]. Attention to detail (e.g., continuous chilling of relevant specimens) is necessary. Recent discovery of hereditary alpha-tryptasemia (HαT (and elsewhere)), a common inheritance of one or more extra copies of the TPSAB1 gene for alpha-tryptase resulting in typically modest, stable elevations in serum tryptase, now requires genetic testing for HAT in MCAS patients with modestly elevated serum tryptase to determine whether such elevations come from MCA (when HAT is not found) or merely reflect germline-programmed slight overexpression of tryptase [not yet proven to be pathogenic, but associated with an increased incidence of MCAS, hEDS, and postural orthostatic tachycardia syndrome (POTS)].

Interpretation of tissue MC counts has remained controversial. Though definitive study is still needed, additional data in recent years suggest consensus-2’s regard of such counts as significant remains reasonable [58, 60, 82, 85, 96]. Some recent studies [56, 57, 119] found no utility of biopsies in diagnosing MCAS (and thus have been asserted to refute consensus-2) but suffered methodologic flaws (e.g., “healthy control” populations not screened to exclude MCAS). Consensus-1 advocates have asserted that, except in mastocytosis, no number of MCs in a biopsy would ever be considered abnormal, a notion which certainly would not apply to other cells and thus likely does not apply to MCs.

Appreciation has increased regarding immune system impacts of MCAS. Insufficiently cautious interpretations of antibody-probing tests in MCAS patients can result in incorrect diagnoses with adverse therapeutic consequences [120].

Even though MCAS can directly drive many symptoms, distinctly recognizable comorbidities both consequent to and independent of MCAS also can be present. The rare inborn autoinflammatory and primary immunodeficiency syndromes can mimic symptoms of MCAS. Patients whose histories suggest such issues warrant genetic testing regardless of whether MCAS is found. Although treatment of MCAS is often successful, expectations with MCAS treatment must remain tempered if other issues remain afoot. When proven MCAS appears “treatment-resistant”, clinicians must consider presence/persistence of MCA triggers and/or comorbidities.

Accurate identification of triggers remains challenging, as is monitoring of treatment response. Triggers may spark MCA flaring via IgE-mediated, IgG-mediated, or other pathways. Triggering of dysfunctional MCs by various exposures may be modulated by dynamic factors (e.g., hormonal fluctuating with menses), leading to startling variances in results from serial iterations of some allergy tests. The accuracy of present clinical laboratory testing for reactivity to medication product excipients and implanted foreign materials remains unclear, requiring cautious clinical usage and interpretation. Such testing nevertheless sometimes can be helpful. Efforts to correlate therapeutic improvements with reductions in mediators tested for diagnosing MCAS generally have been unsuccessful, probably because most symptoms in MCAS stem from aberrant expression of mediators not clinically measurable or not specific to MCs. Advances in objective assessment of MCAS treatment response are needed; response assessment likely will remain dominantly clinical for some time to come.

More details regarding recent diagnostic issues in MCAS (e.g., specifics regarding specimen handling, interpretation of tissue biopsies and antibody tests, overlap with autoinflammatory syndromes, etc.) can be found in Section 2 of the Supplementary Material, Appendix.

Therapeutic issues in MCAS

The complexity of MC biology and heterogeneity of MCAS provide many therapeutic opportunities. Many treatments have proven helpful for various patients. Comprehensive treatment compendia have been published [121, 122]; for reader convenience, an update of one scheme [124] is provided in Figure 1. It seems almost certain that many MCAS variants exist and could be defined through mutational profiling of isolated MCs, but such profiling is not yet clinically available. As such, most MCAS cases continue to be "lumped together" as the single entity of MCAS. Since MCAS variants cannot yet be defined, no evidence-based guidance yet exists for personalizing treatment. However, when physician and patient exhibit patience, persistence, and a methodical approach, the goal of significant sustained improvement is usually reached by assembly of a (usually fairly small, but patient-unique) regimen of MCAS-targeting treatments. Recent therapeutic advances have included new pathobiology-appropriate treatments and increased recognition of issues hampering treatment.

Many chemical and other "foreign material" exposures long thought "inactive" and inconsequential are significant triggers, even at low levels, in some patients in whom treatment successes are limited while trigger exposure continues. Although desensitization therapies may be successful in some cases, elimination of exposure – at least until the MCAS has come to be considerably better controlled – often is the more expedient and effective approach.

Treatment sometimes is hampered by cessation of helpful MCAS-targeting medications due to misinterpretation of recent studies showing increased risk for various morbidities in patients using medications helpful in MCAS (e.g., the reported risk of increased dementia in long-term

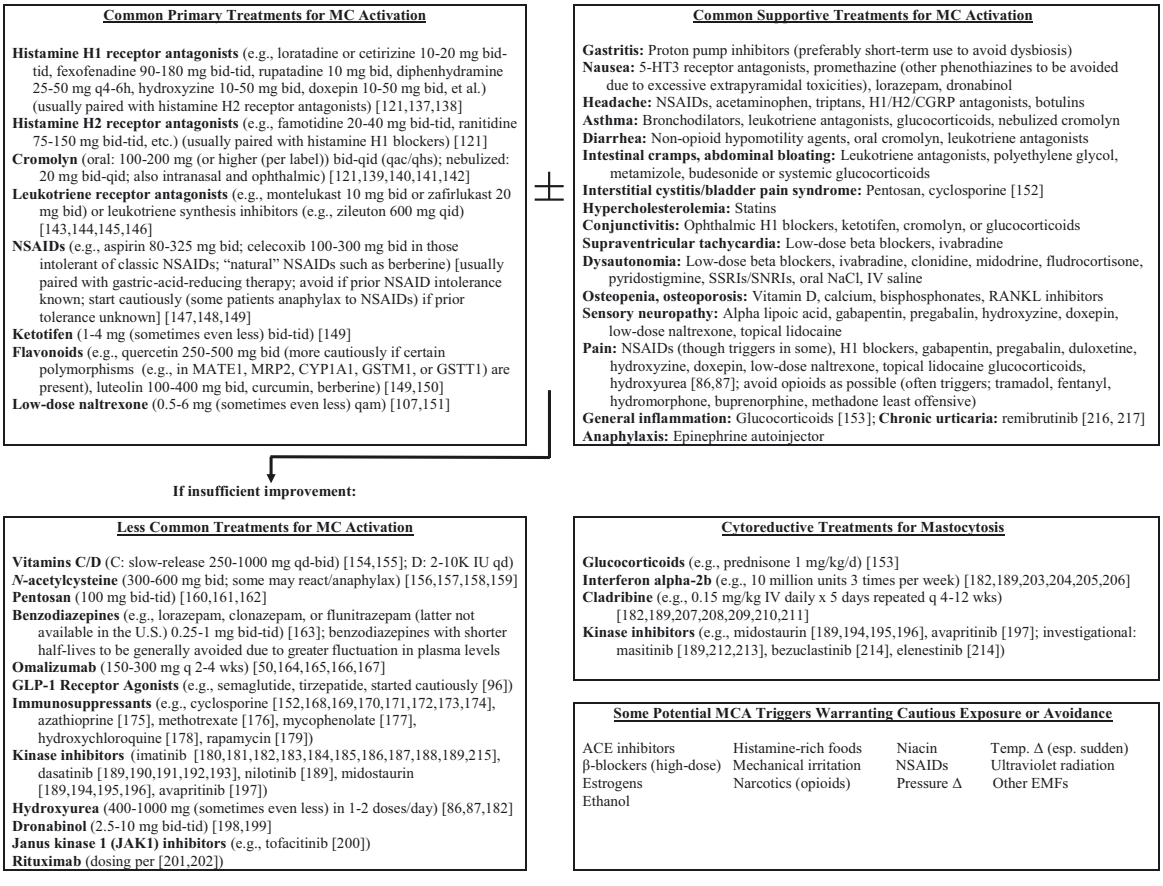

Figure 1: An algorithm for approaching treatment of mast cell activation syndrome (MCAS). Example dosages are for adults. Consider potential interactions of polypharmacy (e.g., curcumin vis-à-vis aspirin, warfarin, clopidogrel, histamine H_2 receptor antagonists, proton pump inhibitors, etc.) do not assume all acute symptoms are due to MCAS; assess acute symptoms in standard fashions. Treatment of MCAS remains largely "trial and error," guided mostly by assessment of the individual patient and the clinician's judgment as influenced by experience. Not every drug listed here will be effective in, or even appropriate to be tried in, every MCAS patient. ACE=angiotensin converting enzyme. CGRP=calcitonin gene-related peptide. EMFs=electromagnetic frequencies. IV=intravenous. MCA=mast cell activation. NSAIDs = non-steroidal anti-inflammatory drugs. RANKL=receptor activator of nuclear factor kappa-B ligand. SNRI=serotonin-norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor.

users of histamine H1 or H2 receptor antagonists) [123–126]. Risk, however, is not a guarantee, and association does not imply causation; we are unaware of any literature showing H1 receptor antagonists (or other commonly used MCAS-targeting drugs examined in these studies) directly cause dementia. Instead, it is possible that hyperactive mast cells may play a role in the pathogenesis of cognitive impairment, raising questions not whether chronic use of MCAS-helpful medications might be associated with increased risk for developing such diseases but rather (1) whether partial control of MCAS with such medications might *decrease* such risk, and (2) whether *earlier recognition and better control* of MCAS might further decrease such risk. Further studies are needed to investigate this hypothesis.

MCAS often causes various dietary intolerances, and MCAS increasingly is being recognized in patients with various eating disorders [127–129]. Furthermore, though MCAS can lead, via a variety of mechanisms, to assorted micronutrient deficiencies, some such deficiencies (e.g., vitamins C and D) can exacerbate MCAS. Increased recognition of these issues may yield clinical fruit.

As more techniques and tools emerge for identifying triggers, new (sometimes even non-pharmacologic) approaches for trigger mitigation are emerging. For example, some MCAS patients learn cyclic migration to avoid seasonal allergens, and avoidance of mycotoxin exposure [130, 131], can be helpful.

Increased recognition of potential for some coagulation disorders (bleeding and/or thromboembolic) [53, 132] and some chronic inflammatory disorders to be rooted in MCAS [53, 133] (or that MCAS is significantly contributing to such disorders) is beginning to lead to consideration of MCAS (diagnostically and therapeutically) in some such patients.

Many new treatments – pharmacologic and non-pharmacologic – with at least anecdotal evidence for being able to improve MCAS have been emerging, too. Increasingly recognized for their anti-inflammatory activities, glucagon-like-peptide-1 (GLP-1) receptor agonists have been reported, anecdotally, as helpful in some MCAS patients [96]. As another example, given that remibrutinib (inhibiting the Bruton tyrosine kinase pathway known to be relevant in MCA) was recently approved for chronic spontaneous urticaria (a disease likely often rooted in MCAS), it becomes possible that remibrutinib might be helpful in MCAS, possibly even for symptoms beyond urticaria. Research is needed to identify such treatments' roles in MCAS, a disease of much broader spectrum than the approved indications.

More details regarding recent therapeutic issues in MCAS (e.g., alleged toxicities of chronic MCAS-targeting treatments, micronutrient deficiencies, newly emerging treatments, etc.) can be found in Section 3 of the Supplementary Material, Appendix.

Research issues in MCAS

Largely due to unawareness of this prevalent disease, little research in MCAS has been done or is underway. Hopefully, research will increase as awareness increases. Although the pharmaceutical industry is motivated to develop better treatments for a prevalent disease which presently has no specifically approved medications, the human and financial costs of MCAS to society and to all public and private health insurers make it even more appropriate for these interests, too, to fund MCAS research.

As noted previously, lack of methods to objectively monitor treatment response is a barrier to therapeutic research, but patient-reported outcomes may be sufficient while more objective assessments remain unavailable [134, 135]. No validated patient-reported symptom assessment tool for comprehensive assessment of an MCAS patient's symptoms has yet emerged, but the authors are aware of one such tool being developed.

Although genetic research begun nearly 20 years ago at one laboratory quickly identified that most MCAS patients have somatic variants in KIT and other MC-regulating genes [9, 10] such findings have not yet been independently confirmed, not because such efforts have been pursued and failed but rather because such efforts have not been pursued (or were not completed [136]). There is ample potential for exploring intersections of MCAS with many associated disorders, investigating the proportion of the population with the associated disease which meets diagnostic criteria for MCAS and whether such populations harbor specific somatic mutational profiles in their MCs, helping direct research in disease mechanisms and treatments. MCAS-oriented directions for further research in such diverse areas as chronic fatigue syndrome, postural orthostatic tachycardia syndrome, hEDS, long-Covid syndrome, and other chronic multisystem inflammatory diseases could emerge from MCAS-exploring pilot studies of 20–30 patients with each of these diseases/disorders.

Hopefully, genetic dissection of MCAS will enable identification of specific variants, a feat which patient histories, physical exams, and available laboratory tests have not yet permitted. Variant information at the mutational level not only might obviate challenging mediator testing but also seems likely to foster personalized therapy.

Still to be defined are the mechanisms by which somatic genetic variants emerge in MCAS. Preliminary research suggests heritable epigenetic variants (creating a fundamental

genomic fragility rendering the genome more susceptible to sustaining somatic variants induced by various insults, such as stressor-driven cytokine storms) may be one root mechanism, but more research is needed.

Discussion

Time affords perspective. Since consensus-2 emerged six years ago, it has become clear that many patients who do not meet consensus-1 criteria but do meet consensus-2 criteria are significantly helped by MCAS-targeting treatments inaccessible without a diagnosis of MCAS. Multiple articles have contended that overdiagnosis of MCAS by broader criteria will bring erroneous and excessive treatment [27, 28, 39–42, 62]. One article [62] assessing MCAS diagnostic criteria even purported to discuss problems from overdiagnosis and from underdiagnosis but then only discussed potential harms of overdiagnosis (i.e., did not address underdiagnosis at all) and further asserted that increased demand for health care from feared (but not yet observed) overdiagnosis justifies restrictive diagnostic criteria. No study, or even case report, demonstrating overdiagnosis (let alone harms from such) has been published. Despite such objections to consensus-2, our experience is that consensus-2 has been used by many practitioners of many specialties around the world to help thousands of patients, most of whom would not meet other diagnostic schemas for MCAS despite their MCAS-consistent presentations and their consensus-2-satisfying laboratory testing. We have seen no overdiagnosis or increased demand for health care from such. If anything, and perhaps unsurprisingly, in our experience accurate diagnosis and effective therapy seems to decrease our MCAS patients' consumption of health care. We feel underdiagnosis – principally due to ongoing physician unawareness of MCAS but also somewhat to use of restrictive criteria for diagnosing it – remains substantial, not only impeding patients from accessing disease-appropriate treatments but also driving clinicians to waste resources trying to treat symptoms without recognizing, let alone treating, the underlying condition.

We have observed, too, it is common that physicians do not follow consensus-1 criteria by asking the patient to pursue repeat tryptase testing during an attack. Instead, the patient often has a single tryptase level determined at (always symptomatic) baseline, and when it (usually) is found to be normal, the patient often is informed this result excludes MCAS. There are a few small studies which document "20 % + 2" rise in serum tryptase during certain types of symptom flares [63–65]. In some of these studies, it is unclear if the higher level was determined in a blood sample drawn within the 4 h limit, after onset of the symptoms, as required by consensus-1, and in none of these studies is there any clarity as to whether baseline serum tryptase was determined at the "asymptomatic" point required by consensus-1. Across our thousands of MCAS patients, we have never seen one who is truly asymptomatic at any point. Instead, they often are at their "baseline" or "usual" level of health (i.e., their personal "normal"), but that baseline is always symptomatic in multiple fashions to various degrees. The complexity of MC biology and heterogeneity of MCAS pathobiology makes it illogical to exclude the diagnosis based on absence of one particular issue (anaphylaxis) or one particular mediator elevation (tryptase) [53], particularly when other clinical and laboratory evidence supports MCAS as the best diagnosis accounting for the largest extent of the patient's course.

We feel that when (1) MCAS can be reasonably included in the differential diagnosis for the patient at hand, (2) MCAS is the differential diagnosis which better accounts than any of the other differential diagnoses for the largest range of findings in the patient's history and physical exam, and (3) the patient can be shown to meet any peer-reviewed published proposed diagnostic schema for MCAS, then it is reasonable to diagnose MCAS and to attempt to treat it. If another diagnosis later becomes apparent which even better accounts for all the findings in the patient (including demonstrable MCA), then the new diagnosis should become the primary diagnosis and treatment should pivot accordingly. However, until discovery of a better diagnosis, persistence at efforts to treat MCAS in a patient who has met any published diagnostic schema for MCAS seems reasonable, with the understanding that the aforementioned great heterogeneity in pathobiology ensures there will be great heterogeneity in treatments found efficacious – thus necessitating persistence by physician and patient in trying sensible options. Responses to most MCAS-targeting drugs are seen quickly, allowing timely elimination of ineffective treatments and retention only of significantly helpful treatments to craft the patient's optimal regimen. Advancing science and testing eventually will permit identifying specific MCAS variants, leading to more efficient and effective treatment. Until then, it remains better to establish a sensible diagnosis and find effective treatment for a disease which may be endured for the rest of the patient's life. Lack of diagnosis facilitates harmful dismissal and gaslighting.

All clinicians (and trainees) and laboratory, pharmaceutical, and health insurance industries, governmental health care agencies, and health care research organizations need to learn about MCAS. Many patients continue reporting their local practitioners lack awareness of MCAS or deny it exists (or confuse it with mastocytosis or assert the patient "cannot have it because it is rare"). Although allergy/

immunology training programs have begun providing trainees some education about MCAS, most training programs remain unaware of the disease. The first teaching about MCAS provided to undergraduates (freshman medical students) was delivered at the University of California at Irvine in May 2025, providing a model for other schools. Time will tell how these trainees' recognition of possible MCAS in their patients is received by their supervisors who have not yet come to know MCAS. Ultimately, awareness of MCAS will broaden, and students will become teachers, leading to widespread acceptance and recognition of MCAS just as with many other significant developments in the history of medicine.

Improvement of education and research will benefit from organized approaches leveraging expertise in MCAS in the form of clinicians who never received formal training about MCAS but have nevertheless acquired extensive experience. Although some organizations conducting research in the MCAS arena [e. g., the European Competence Network in Mastocytosis (ECNM, https://innere-med-1.meduniwien.ac.at/unsere-klinischen-abteilungen/haematologie-und-haemostaseologie/projekte/ecnm-registry-european-competence-network-mastocytosis/) and the American Initiative in Mast Cell Disorders (AIM, https://aimcd.net/)] have helped define, and have adopted, a consensus-1-based approach to MCAS, another such organization, the International Society for Mast Cell Activation Syndromes (ISMCAS, https://ismcas.org/), has more recently emerged and embraced a consensus-2-based approach to the disease. Also, as awareness of MCAS has been increasing in the patient community, mast cell disease patient support organizations have been increasing their presence and activities, including The Mast Cell Disease Society (https://tmsforacure.org/) and Super T's Mast Cell Foundation (https://supertmastcell.org/) in the U.S. as well as similar organizations in many other countries around the world (a comprehensive list is available at https://mastocytosis-mcas.org/support/).

Conclusions

A consensus-2-based approach to diagnosing MCAS continues to enable diagnosis and successful treatment in many patients not meeting other diagnostic schemas. Consensus-2-enabled overdiagnosis has not been observed, but underdiagnosis remains a frequent, significant problem. Most MCAS patients find treatment which gains them better quality of life for the remainder of a normal life span, so establishing diagnosis (to gain access to treatment) remains a major barrier. Until more research allows clarification of optimal diagnostic criteria, prioritization of patients' interests compels physicians to use consensus-2 diagnostic criteria for MCAS to establish diagnosis in any patient with presentation inviting consideration of MCAS.

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