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Mast Cell Activation Disease and Microbiotic Interactions

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ABSTRACT

Purpose: This article reviews the diagnostically challenging presentation of mast cell activation disease (MCAD) and current thoughts regarding interactions between microbiota and MCs.

Methods: A search for all studies on interactions between mast cells, mast cell activation disease, and microbiota published on pubmed.gov and scholar.google.com between 1960 and 2015 was conducted using the search terms mast cell, mastocyte, mastocytosis, mast cell activation, mast cell activation disease, mast cell activation syndrome, microbiome, microbiota. A manual review of the references from identified studies was also conducted. Studies were excluded if they were not accessible electronically or by interlibrary loan.

Findings: Research increasingly is revealing essential involvement of MCs in normal human biology and in human disease. Via many methods, normal MCs—present sparsely in every tissue—sense their environment and reactively exert influences that, directly and indirectly, locally and remotely, improve health. The dysfunctional MCs of the "iceberg" of MCAD, on the other hand, sense abnormally, react abnormally, activate constitutively, and sometimes (in mastocytosis, the "tip" of the MCAD iceberg) even proliferate neoplastically. MCAD causes chronic multisystem illness generally, but not necessarily, of an inflammatory ± allergic theme and with great variability in behavior among patients and within any patient over time. Furthermore, the range of signals to which MCs respond and react include signals from the body's microbiota, and regardless of whether an MCAD patient has clonal mastocytosis or the bulk of the iceberg now known as *MC activation syndrome* (also suspected to be clonal but without significant MC proliferation), dysfunctional MCs interact as dysfunctionally with those microbiota as they interact with other human tissues, potentially leading to many adverse consequences.

Implications: Interactions between microbiota and MCs are complex at baseline. The potential for both pathology and benefit may be amplified when compositionally variant microbiota interact with aberrant MCs in various types of MCAD. More research is needed to better understand and leverage these interactions. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: mast cell, mast cell activation disease, mast cell activation syndrome, mastocytosis, microbiota.

INTRODUCTION

First identified in 1863, mast cells (MCs, from the German *mastzellen,* or "well-nourished cells," from rich granular content seen on metachromatic staining) soon were associated with disease in the rare neoplastic skin malady urticaria pigmentosa and then a half-century later with even rarer internal neoplasia, now called *systemic mastocytosis* (SM).[1] MCs crucially effect and regulate adaptive and innate immunity. The identification of variably expressed signaling molecules, or "mediators," in MCs began in 1937 with heparin. More than 200 MC mediators are known (although few specific to MCs), including tryptase, histamine, and certain prostaglandins and leukotrienes.[2] MCs secrete prestored mediators and synthesize mediators in response to allergic, microbial, and nonimmune triggers. Widely, sparsely distributed, and of hematopoietic origin, MCs essentially contribute to many processes, including defense, growth, and healing. Among the oldest host defense cells, putatively arising in multicellular eukaryotes some 500 million years ago,[3] MCs possess large arrays of potent sensory and response mechanisms, with tissue-specific sensitivities

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activating numerous intracellular pathways intersecting to modulate the quality and magnitude of response. Best characterized among MC activation mechanisms is antigenic cross-linking of immunoglobulin (Ig) E bound to MC-surface high-affinity IgE receptor (FcεRI). MCs also express G-protein–coupled receptors and other IgE-independent recognition sites. Basic insights into MC biology continue emerging, including the recent recognition that serum tryptase reflects more the body's MC load than activation state.[1]

Apart from the involvement in allergy, MCs leverage mediators to crucially assist in maintaining integrity and function in all tissues.[2] MCs regulate defense by acting as innate immune cells, by interacting with the specific immune system, and by inducing and regulating inflammation.[2] MCs orchestrate microbial, toxic, and physical environmental defenses and recruit other immune cells to injury sites.[2] MCs regulate homeostasis, too, contributing crucially to tissue remodeling, including wound healing.[2] MCs promote homeostasis by degrading endogenous and bacterial toxins.[2] MCs release mediators via classic degranulation, selective secretion ("piecemeal" or "differential" degranulation), and transgranulation.[4,5] Evolutionary success of these mechanisms is due to fine regulation, inferring potential for multisystem havoc from dysregulated MCs.

Classic thought attributed much of allergy to aberrant MC reactivity, while constitutive activation drove MC neoplasia (cutaneous mastocytosis [CM], SM, and rare solid MC tumors). We now understand that frankly malignant MC proliferation drives stark MC accumulation in aggressive forms of mastocytosis, whereas antiapoptosis drives modest accumulations seen in more common, indolent forms of mastocytosis.[1] Speculation about MC disease featuring constitutive activation without neoplasia emerged in 1991[6]; case reports were first published in 2007.[7,8] Crucial insight into the marked clinical heterogeneity of relatively nonproliferative MC activation syndrome (MCAS) came with the discovery of many mutations in MC Kit mRNA in a cohort of patients with MCAS (findings later extended including healthy controls largely absent such mutations).[9,10] Multiple investigators soon reported that most mastocytosis cases, too, harbor multiple mutations across many MC regulatory genes, epigenes, and microRNAs.[1]

Expressed 10-fold brighter in MCs than any other human cells, transmembrane tyrosine kinase KIT is the dominant MC regulator.[2] Binding of stem cell factor to homodimeric KIT conformationally changes the intracellular domains of KIT, effecting autoinhibition at the juxtamembrane domain and activation of kinase domains, consequently promoting MC survival, mediator production and release, and other functions. Thus, varied constitutively activating mutational patterns in MC KIT would be expected to produce varied clinical presentations. KIT^{D816V} is consistently found in SM (>90% of cases)[2] and likely drives prominent pathologic features, including MC proliferation, aggregation, spindling, tryptase overexpression, and CD25 coexpression.[2] However, repeated findings that patients with MCAS harbor multiple mutations in KIT, albeit in no yet-apparent recurrent patterns[9,10] (and almost never including KIT^{D816V}), together with similar mutational heterogeneity in KIT and other MC regulatory elements in patients with mastocytosis,[11] align with observations of marked clinical heterogeneity in patients with MCAS and mastocytosis. Although MCAS appears usually clonal in the research laboratory, most commercial laboratories today assess MC clonality only by KIT mutation analysis at codon 816 (via polymerase chain reaction) or by MC CD25 or CD2 expression (by flow cytometry). As these signatures appear rare in MCAS, diagnosis presently rests on finding elevated MC mediator levels and excluding differential diagnoses.

Like most neoplasms, mastocytosis usually stems from somatic mutations; germ line mutations are rare.[11] MCAS appears similar.[11,12] Yet, a familial predisposition for MC activation disease (MCAD) has been demonstrated.[11,13] Complexity multiplies on recognition that different affected members of an affected kindred usually bear disparate presentations and MC mutational profiles. Perhaps inheritable epigenetic mutations create genetic fragility states susceptible to specific stressors, inducing specific (and/or random?) stem cell or progenitor mutations principally operant in MCs. Evidence for epigenetic pathogenicity in MCAD is emerging; patients with MCAD bear abnormal epigenomes.[11,12,14] However, lifestyle-influenced factors, such as diet; alcohol use; and, yes, microbiota,[15,16] may influence MCAD phenotype.

In 2010, the recognition that all MC disease manifests aberrant MC activation engendered new top-level designation of MCAD encompassing all pathologic MC states.[1] Rare, proliferative CM and SM compose one element of MCAD, while forms of (relatively nonproliferative) MCAS compose other elements of

MCAD. Except in aggressive mastocytoses, the distinctions between MCAS and mastocytosis are principally pathologic (eg, significantly elevated serum tryptase and gross MC proliferation present in mastocytosis but absent in MCAS) and appear clinically inconsequential. Two proposals, of varying strengths, for MCAS diagnostic criteria have emerged (Figure 1).[17] The diagnosis and treatment of MCAD are complex; interested readers should consult recent reviews.[1,2,17]

Truly reactive/secondary MCAS is increasingly difficult to identify given rising recognition that diseases previously thought to provoke MC activation may actually be sparked by primary MCAS. It seems likely that given presentations of mastocytosis and primary MCAS result from specific mutation sets driving specific patterns of aberrant constitutive MC activation as well as aberrant MC reactivity, the effects of which may be direct and/or indirect as well as local and/or remote, ultimately affecting normal cells, other abnormal MCs, and other abnormal cells potentially harboring similar mutations. Effects in these other cells may "rebound," too, to further activate the instigating abnormal MCs. Presently, commercial probing for MC mutations is very limited (essentially only KIT^{D816V}). Although some subclassify MCAS as primary (clonal), secondary (reactive), and idiopathic[1] (or nonclonal[18]), perhaps subclassification as clonal and undetermined clonality is more accurate. When readily commercially available, whole genome/exome sequencing of isolated MCs may prove instructive.

Thus, after 150 years of orthodoxy that MC disease is principally allergic phenomena and neoplastic mastocytosis, it is now evident that such entities merely "cap" an MCAD "iceberg" (Figure 2), with non-neoplastic MCAS composing the largely unrecognized bulk of MCAD for reasons reviewed subsequently.

As recognition of MCAD/MCAS has expanded, so, too, has recognition of the importance of human microbiota to health and disease, including crucial interactions with MCs. Below we review highlights of MCAD and current thoughts regarding microbiotic interactions with MCs and MCAD.

MATERIALS AND METHODS

A search for all studies on interactions between mast cells, mast cell activation disease, and microbiota published on pubmed.gov or scholar.google.com between 1960 and 2015 was conducted using the search terms mast cell, mastocyte, mastocytosis, mast cell activation, mast cell activation disease, mast cell activation syndrome, microbiome, microbiota. A manual review of the references from identified studies was also conducted. Studies were excluded if they were not accessible electronically or by interlibrary loan.

RESULTS

A total of 140 studies were identified and included in the present review. Studies not specifically cited were excluded due to redundancy of results and citation limits.

Mast Cell Activation Disease

Epidemiology, Natural History, Prognosis, and Familial Considerations

Mastocytosis is rare. The estimated incidence in western Europe is 5 to 10 per 1 million population per year[19,20]; the prevalence is 0.3 to 13 to 100,000.[11] Only preliminary epidemiologic data on MCAS have been reported. In Germany, the prevalence of MCAD has been estimated at 5% to 10% of the general population,[11–13] which may be unsurprising because MCAS may underlie many common conditions in subsets of patients, such as those with fibromyalgia and irritable bowel syndrome (IBS).[2] CM cases outnumber SM by 10 to 1.[12] Most CM presents in childhood, commonly spontaneously regressing by late adolescence, but later emergence of possibly MCAS-attributable illnesses calls into question whether spontaneous cure truly occurs.

Mastocytosis occurs equally in males and females[21]; in MCAS, females seemingly prevail by 3 to 1,[12] but given only recent recognition of MCAS and the erratic, nebulous, generally non-life-threatening symptoms of MCAD, affected males may underpresent. No racial predilection is known.

SM typically emerges in middle age or later. In MCAS, symptoms typically first manifest in adolescence or earlier. Most MCAD symptoms are nonspecific, recognized only in retrospect as MCAD related; careful history often finds decades of latency between symptom onset and diagnosis in SM and MCAS.[1,2,22,23]

MCAD naturally features periods of relatively stable symptoms (waxing and waning somewhat but also occasionally with unpredictable, potentially severe acute flares), punctuated by often permanent stepwise escalations in baseline symptom profiles soon after major stressors both predictably physiologic

WHO 2008 Diagnostic Criteria for Systemic Mastocytosis

Major Criterion:

1. Multifocal, dense aggregates of MCs (15 or more) in sections of bone marrow or other extracutaneous tissues and confirmed by tryptase immunohistochemistry or other special stains

Minor Criteria:

1. Atypical or spindled appearance of at least 25% of the MCs in the diagnostic biopsy
2. Expression of CD2 and/or CD25 by MCs in marrow, blood, or extracutaneous organs
3. KIT codon 816 mutation in marrow, blood, or extracutaneous organs
4. Persistent elevation of serum total tryptase > 20 ng/ml

Diagnosis of SM made by either (1) major criterion + any one or more minor criteria, or (2) any three minor criteria.

Proposed Diagnostic Criteria for Mast Cell Activation Syndrome

Valent et al. Criteria

1. Chronic/recurrent symptoms (flushing, pruritus, urticaria, angioedema, nasal congestion or pruritus, wheezing, throat swelling, headache, hypotension, and/or diarrhea) consistent with aberrant MC mediator release
2. Absence of any other known disorder that can better account for these symptoms
3. Increase in serum total tryptase of [20% above baseline, plus another 2 ng/ml] during, or within 4 hours after, a symptomatic period
4. Response of symptoms to histamine H_1 and/or H_2 receptor antagonists or other "MC-targeting" agents such as cromolyn.

Molderings et al. Criteria

Major Criteria:

1. Multifocal MC aggregates as per WHO major criterion for SM
2. Clinical history consistent with chronic/recurrent aberrant MC mediator release

Minor Criteria:

1. Abnormal MC morphology as per WHO SM minor criterion #1
2. CD2 and/or CD25 expression as per WHO SM minor criterion #2
3. Detection of known constitutively activating mutations in MCs in blood, marrow, or extracutaneous organs
4. Elevation in serum tryptase or chromogranin A, plasma heparin or histamine, urinary N-methylhistamine, and/or other MC-specific mediators such as (but not limited to) relevant leukotrienes (B4, C4, D4, E4) or PGD_2 or its metabolite 11-β-$PGF_{2\alpha}$.

Diagnosis of MCAS made by either (1) both major criteria, or (2) the second major criterion plus any one of the minor criteria, or (3) any three minor criteria.

Figure 1. Diagnostic criteria for systemic mastocytosis (SM) and mast cell activation syndrome (MCAS).[17] PG = prostaglandin; WHO = World Health Organization.

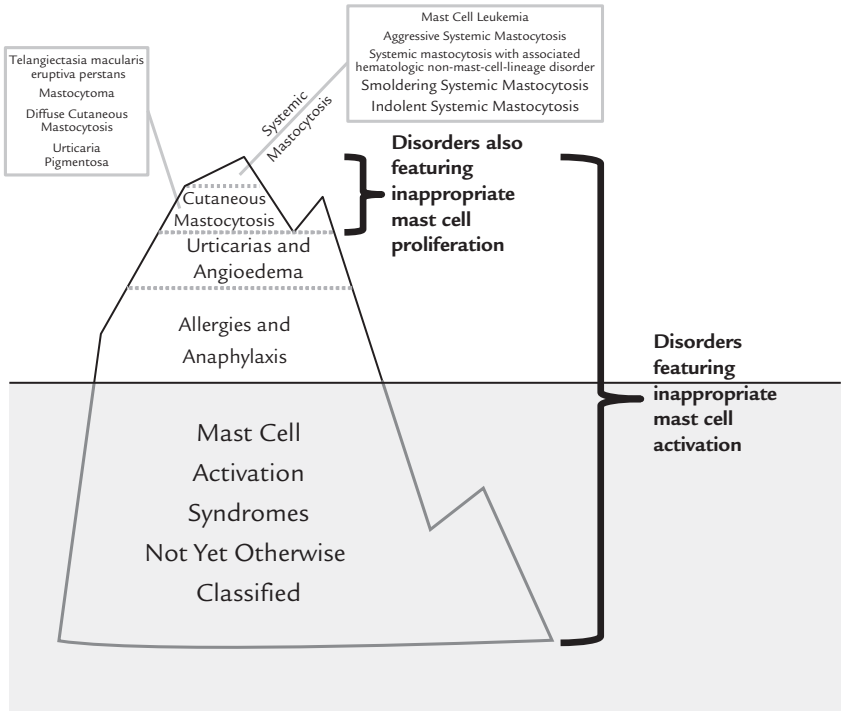

Figure 2. An iceberg-type metaphoric conception of the spectrum of disorders of mast cell (MC) activation, with typically vividly presenting entities arrayed above a "waterline" of relatively easy clinical recognizability in order of estimated prevalence.[1] The most recently recognized entity, MC activation syndrome (MCAS), with recent preliminary prevalence estimates of 5% to 10%, may be "hidden below the waterline," or more difficult to clinically recognize, due to heterogeneity of presentation, fewer visually distinctive signs, and other factors. The various forms of mastocytosis are mutationally rooted, primary MC diseases, as are rare variants of MCAS which can be proven monoclonal (although clinical laboratory testing for such at present is largely constrained to [1] probing by polymerase chain reaction for the constitutively activating KIT^{D816V} mutation, and [2] testing by flow cytometry for MCs bearing pathognomonically aberrant $CD117^{+}CD25^{+}$ or $CD117^{+}CD2^{+}$ signatures, which, when present, often compose very small portions (<1%) of the tested cell population). Other classic MC-activation disorders have long been thought to be secondary/reactive MC diseases, although more extensive mutational analyses have suggested recently that most MCAS cases, like mastocytosis, are also mutationally rooted.

(eg, puberty) and unpredictably pathologic (eg, physical/psychological trauma, infection). Such escalations possibly reflect subclonal evolution. Eventually, paucisymptomatic periods shorten and chronic symptoms intensify. Careful history taking in patients with MCAD usually shows that patients rarely are truly symptom-free and commonly identifies a major stressor or novel exposure shortly antedating a general decline in health leading to presentation. Such patients sometimes are convinced that the stressor/exposure caused the illness, but careful history usually reveals MCAD-attributable symptoms present long before the "turning point."

Expected life span is normal with indolent SM (~90% of SM).[21,24,25] Advanced mastocytosis (SM with eosinophilia or associated hematologic malignancy, aggressive SM, and MC leukemia) confers worse survival (as short as 6 months with MC leukemia),[21,23,24] although investigational therapies appear promising. Aggressive SM features, so-called "B- and C-findings," reflect larger MC loads, expansion of genetic defects into other myeloid lineages, and

impaired organ function due to MC infiltration.[21,23,24,26] Transformation of indolent SM to advanced types appears rare[27]; MCAS has not been so studied, but the authors have never observed MCAS transform to mastocytosis. Although no formal survival studies have been reported, MCAS appears to course similarly to indolent SM, that is, life of normal span, if morbid until the disease is diagnosed and effectively controlled.

Most MCAD-associated mutations appear somatic,[12] but familial MCAD appears common and may be an epigenetic phenomenon.[13,14] Approximately 75% of index patients with MCAD have at least 1 afflicted first-degree relative,[13] suggesting substantial inheritability. Approximately half of patients with MCAD have children who also appear afflicted to varying degrees,[13] but without predictors of risk for MCAD, no recommendations can be given regarding reproductive decisions.

Clinical Presentation

MCAD presents diversely (**Table**; more detail presented by Afrin[2]) due to widespread MC distribution and great heterogeneity of aberrant mediator expression patterns, potentiating many anomalies in any or all tissues. The nonspecific nature of almost every symptom often foils clinical recognition until decades later, if ever.[1] Symptoms often are "inflammatory"; arise acutely, subacutely, or chronically/developmentally; persist, waxing and waning to varying degrees at unpredictable times; and sometimes remit and then (again, unpredictably) relapse. Given their common absence of histologically detectable MC neoplasia, patients with MCAS often seem inexplicably, chronically, and multisystemically ill, perhaps recognized as having an inflammatory disease but one that does not "fit" any well-known such syndrome. No system is spared potential impact, but there is no certainty that any given system will be affected. Disability is common, sometimes severe.

"Routine" diagnostics often yield normal or equivocal results, or mild to moderate, but ephemeral, abnormalities. Presenting symptoms usually are subtle to moderate but may be severe or even life-threatening (eg, nonatherosclerotic myocardial infarction [often unrecognized as the vasospastic allergic angina of Kounis syndrome], end-stage renal failure, refractory diarrhea), leading to "exhaustive," nondiagnostic testing, whereupon psychosomatism is commonly misdiagnosed (especially if presentation includes classic neuropsychiatric symptoms).[1,2] Reflecting mutational heterogeneity, MCAD can present opposite abnormalities in different patients (eg, diarrhea vs constipation, polycythemia vs anemia) or in a given patient at different times (eg, alternating diarrhea and constipation) or simultaneously (eg, coexisting osteoporosis and osteosclerosis).[1,2] Acute "flares" or "spells" are common, often occasioning urgent evaluations that, although necessary to rule out other illnesses, frequently are unrevealing, heightening suspicions of psychosomatism. Commonly, many idiopathic diagnoses accrue (and respond poorly to treatment) (eg, fibromyalgia, chronic fatigue, neurogenic pain, IBS, hypermobility-type Ehlers-Danlos syndrome, postural orthostatic tachycardia, histamine intolerance, dysautonomia, anxiety/panic, interstitial cystitis [itself often misdiagnosed as culture-negative urinary tract infection]). Some yet-undiagnosed patients with MCAD have definitive comorbidities (eg, sickle cell anemia or obesity) blamed for many symptoms despite difficulty of attribution, by known (patho)biological pathways, of such symptoms to such ailments.[1,2]

Aberrant reactivities may be prolific, odd, and, when medication related, directed against excipients, not active ingredients. Some "allergies" (eg, to iodine or even water!) may seem psychosomatic until the recognition of excipient (eg, povidone in iodine/povidone solution) or physical (eg, temperature) triggers.

Complete history taking helps to establish suspicion for MCAD. History must include a thorough systems review, as many patients with MCAD have ailed for so long that they accept much of their illness as "normal," or they tire or become wary, after so many nondiagnostic evaluations or suspicions of psychosomatism, of reporting certain symptoms.

Interactions between Human Microbiota and Mast Cells

The gut has dominated research on microbiota. Gut microbiota are now recognized as a "microbial organ," interacting extensively with its human host[28] and second only to the liver as the largest metabolic organ in the body, involved in 10% of circulating metabolites,[29] many impacting nervous and immune system function. Recent environmental factors (eg, extensive antibiotic use, increased processed-food consumption) may underlie decreases in microbiotic diversity and metabolic capacity, in turn altering the

Table. Symptoms and findings in mast cell (MC) activation disease.[*2,22,23]

System	Potential Manifestations of Mast Cell Disease
Constitutional	Fatigue, malaise, asthenia, chronic fatigue syndrome, subjective and/or objective hyperthermia and/or hypothermia, sense of "feeling cold much of the time," sweats/diaphoresis (not always nocturnal), flushing, plethora or pallor, increased or decreased appetite, early satiety, weight gain or loss, pruritus, environmental sensitivities (often odd)
Dermatologic	Rashes and lesions of many sorts (classic urticaria pigmentosa, "freckles," telangiectatic/angiomatous lesions, xerosis, warts, tags, folliculitis, ulcers, diffusely migratory but sometimes focally persistent patchy erythema), pruritus (often diffusely migratory, sometimes aquagenic), flushing, angioedema, striae, dermatographism, poor healing
Ophthalmologic	Irritated eyes, increased or decreased lacrimation, suffusion, conjunctivitis, difficulty focusing, lid tremor/tic, solar sensitivity, infectious or sterile inflammation
Otologic	Infectious or sterile otitis externa and/or media, hearing loss or hyperacusis, tinnitus, otosclerosis
Oral/oropharyngeal	Pain (sometimes "burning"), leukoplakia, fibrosis, lichen planus, ulcers, sores, angioedema, dental decay, dysgeusia, throat tickle/discomfort/irritation/pain, postnasal drip
Lymphatic	Adenopathy, usually sub-pathologic and often waxing/waning in size, sometimes asymptomatic but not uncommonly tender, sometimes focal, sometimes migratory, pathology usually shows a reactive lymphocytosis or sometimes an atypical non-specific lymphoproliferative disorder; left upper quadrant discomfort (likely from release of mediators from splenic MCs with or without detectable splenomegaly)
Pulmonary	Rhinitis, sinusitis, pharyngitis, laryngitis, bronchitis, pneumonitis (often confused with infectious pneumonia), cough, dyspnea (often low-grade, inconstant, "I just can't catch a deep breath" despite normal pulmonary function tests), wheezing, obstructive sleep apnea, pulmonary hypertension
Cardiovascular	Presyncope (lightheadedness, weakness, dizziness, vertigo) and/or syncope, hypertension and/or hypotension, palpitations, dysrhythmias, chest discomfort or pain (usually non-anginal in character), coronary and peripheral arterial atherosclerosis/spasm/infarction, aneurysms, hemorrhoids, varicosities, aberrant angiogenesis (hemangiomas, arteriovenous malformations, telangiectasias), migratory edema (often non-dependent and in spite of normal cardiac and renal function)
Gastrointestinal	Aerophagia, angioedema in any segment of the luminal tract, dysphagia (often proximal, possibly due to pharyngeal angioedema), pain/inflammation (often migratory) in one or more segments of the luminal tract (from esophagitis to proctitis) and/or one or more solid organs (eg, hepatitis, pancreatitis), queasiness, nausea, vomiting, diarrhea and/or constipation (often alternating), malabsorption (more often selective micronutrient malabsorption than general protein-calorie malabsorption), ascites either from portal hypertension and/or peritoneal serositis; gastroesophageal reflux disease (often "treatment refractory") and inflammatory/irritable bowel syndrome are common preexisting diagnoses
Genitourinary	Inflammation (often migratory) in one or more segments of the luminal tracts (ureteritis, cystitis, urethritis, vaginitis, vestibulitis) and/or one or more solid organs

(continued)

Table. (continued).

System	Potential Manifestations of Mast Cell Disease
	(eg, nephritis, prostatitis), chronic kidney disease, endometriosis, chronic low back pain or flank pain or abdominal pain, hydronephrosis (likely from ureteral angioedema), infertility, erectile dysfunction, decreased libido; in the appropriate setting of multisystem morbidity, miscarriages should prompt consideration of antiphospholipid antibody syndrome potentially due to MCAS
Musculoskeletal	Clinical myositis, often diffusely migratory (fibromyalgia is a common pre-existing diagnosis), subclinical myositis (i.e., asymptomatic elevated creatine kinase not otherwise explained), arthritis (typically migratory), joint laxity/hypermobility, osteoporosis/osteopenia, osteosclerosis, sometimes mixed osteoporosis/osteopenia/osteosclerosis; MCAS-driven musculoskeletal pain not uncommonly is poorly responsive to NSAIDs and narcotics
Neurologic	Headache (especially migraine), presyncope and/or syncope, peripheral (usually distal) sensory and/or motor neuropathies including paresthesias, tics, tremors (typically resting), chronic inflammatory demyelinating polyneuropathy, seizure disorders (can be "treatment-refractory")
Psychiatric	Mood disturbances (eg, anger, depression), bipolar affective disorder, attention deficit-hyperactivity disorder, post-traumatic stress disorder, other anxiety and panic disorders, psychoses, memory difficulties, word-finding difficulties, other cognitive dysfunction, wide variety of sleep disruptions
Endocrinologic/ Metabolic	Abnormal electrolytes (including magnesium) and liver function tests, delayed puberty, dysmenorrhea, endometriosis, osteosclerosis and/or osteoporosis, hypothyroidism, hyperthyroidism, dyslipidemia, hyperferritinemia, selective vitamin and/or other micronutrient deficiencies, weight change, possibly diabetes mellitus
Hematologic/ Coagulopathic	Polycythemia or anemia, leukocytosis or leukopenia, chronic (usually mild) monocytosis or eosinophilia or basophilia, thrombocytosis or thrombocytopenia, arterial and/or venous thromboembolic disease, aberrant bruising and bleeding; in MCAS the marrow usually does not show increased or even flow-cytometrically aberrant MCs and marrow histology is often interpreted as normal or as unspecified myelodysplastic/myeloproliferative syndrome; standard cytogenetic studies are almost always normal or show culture failure
Immunologic	Type I, II, III, and IV hypersensitivity reactions (eg, allergy, delayed-type hypersensitivity, etc.), increased risk for malignancy, autoimmunity, impaired healing, increased susceptibility to infection, elevated or decreased levels of one or more isotypes of immunoglobulin; modest monoclonal gammopathy of undetermined significance not uncommon

*Most symptoms and findings are chronic and low grade; some are persistent; many are either episodic or waxing/waning.

function of MCs which, via their proximity to nervous and endocrine system elements, crucially regulate intestinal permeability, visceral sensitivity, and gastrointestinal motility.[30–34]

Among key end-products of microbial fermentation of complex polysaccharides in the distal gut, short-chain fatty acids (SCFAs) (eg, butyrate, propionate, acetate) calorically nourish colonocytes and communicate, via specific cell-surface G-protein receptors, with many host cells, including MCs.[35,36] SCFAs inhibit histone deacetylation, modulating cell function through epigenetic changes (a crucial mechanism for the induction of colonic regulatory forkhead box P3 [FoxP3]$^{+}$CD4^{+} T cells)[37–39] and inhibiting MC histamine release.[40] Butyrate inhibits

MC degranulation and tumor necrosis factor-α production.[41]

Microbial carbohydrate products (eg, *S*-type lectins such as galectins and I-type lectins such as Siglecs) affect MCs. The expression of FcεRI-dependent histamine and prostaglandin D_2 release was blocked by the binding of microbial metabolite Siglec-8 with MCs.[42] MCs from galectin-3–deficient mice secrete less histamine and interleukin-4 on FcεRI cross-linking.[43] Extracellular galectin-3 induces apoptosis in MCs, while galectin-1 and -9 reduce the ability of MCs to degranulate, possibly due to inhibition of IgE–antigen complex formation.[44]

The proximity of degranulated MCs to enteric glia has engendered hypotheses that stress activates the enteric nervous system, attracting and activating MCs.[29,30] Stressed rats develop gastrointestinal tract mucosal MC hyperplasia.[45] Acute stress stimulates intestinal mucus secretion by a MC-dependent mechanism.[43] Stress causes rat colonic epithelial barrier defects and subsequent mucosal MC activation.[46] Decreased barrier function may result in greater exposure to microbiota, promoting migration of MCs into intestinal tissue.[16] Commensal bacteria suppress in vitro degranulation of MCs.[16] As reviewed by Wesolowski and Paumet,[47] bacteria differentially regulate secretion of MC-derived mediators. *Mycoplasma pneumoniae* and *Streptococcus pneumoniae* induce MC degranulation, whereas probiotics inhibit degranulation in human and mouse MCs. Impacts of any given bacterium likely are not so 1-sided, though. In mice, *Escherichia coli* attenuates serotonin and β-hexosaminidase secretion but induces histamine release. Molecular mechanisms of such modulation are largely unexplored, but Wesolowski and Paumet reported that *E coli* profoundly decreases synaptosomal-associated protein 23 phosphorylation and ternary soluble N-ethyl maleimide-sensitive fusion protein attachment protein receptor complex assembly, both required for MC granule exocytosis, thus inhibiting FcεRI-dependent degranulation.[46] Altered motility patterns and abdominal pain in postinfectious IBS are associated with MC secretions such as tryptase and serotonin.[48] Urinary *N*-methylhistamine, marking MC activation, is increased in patients with IBD[49] and in animal models.[50] In rats, alcohol ingestion alters the colonic mucosal epithelial barrier via ethanol oxidation into (MC-activating) acetaldehyde by enteric microflora.[51] Chronic alcohol consumption modifies human gut microbiota, causing endotoxemia and immune system hyperactivation, which contribute to liver disease[52] and are all the more interesting in view of the frequency of hepatic abnormalities in MCAS.[53] Alcohol has complex effects on MCs: Alcohol-related immunosuppression may be due in part to MC inhibition[54] and even apoptosis[15] by alcohol (or its metabolites), but in some circumstances alcohol and its metabolites (or preservatives such as sulfites) activate MCs,[55–57] which may be unsurprising given the intolerance that many patients with MCAD have for alcohol.[58,59]

Dietary management is important in IBS. The most successful diet (FODMAP [fermentable oligosaccharides, disaccharides, monosaccharides, and polyols]) decreases colonic gas and SCFA production.[60] Many studies show increased colonic mucosa MCs in diarrhea-dominant and postinfectious IBS[30,32,61–64] and sometimes in constipated IBS.[65] Several small clinical trials suggest roles for MC stabilizers in IBS.[66–68]

Medications, too, affect microbiota and their MC interactions. In compensated cirrhotic patients, omeprazole is associated with microbiotic shift and functional change in distal gut, engendering bacterial overgrowth.[69] Compared with untreated controls, mice treated with antibiotics to reduce gut microbiota and then exposed to *Aspergillus* spp developed increased MCs.[70] Amoxicillin-induced microbiotic changes reduce the expression of major histocompatibility complex class I and II genes in the small and large intestines, reduce adenosine monophosphate expression in the proximal intestine, and increase MC protease expression in the distal small intestine.[71] Mouse microbiotic alterations from broad-spectrum antibiotics or germ-free conditions cause a switch from IgA to IgE and subsequent MC activation.[72]

Microbiotic manipulations can reduce normal MC activation. The probiotic lysate significantly inhibits capsaicin-induced calcitonin gene-related peptide release by neurons and improves signs of inflammation.[73] A humanized mouse model fed high fat plus probiotics exhibited significantly fewer intestinal MCs and multiple other antiinflammatory effects compared with identical mice not provided probiotics.[74] There are increasing suggestions, too, that microbiotic manipulations may be able to prevent colorectal cancer,[75] an effect possibly dependent on microbiotic interactions with MCs and perhaps unsurprising given

not only long-recognized associations between MC activation and initiation and progression of cancer[76,77] but also an ability to improve outcomes of human malignancies on recognition and treatment of comorbid SM[78] or MCAS.[79]

Beyond the gut are microbiota of the skin, lungs, sinuses, and mouth. The involvement of MCs in these other networks is just beginning to be defined. Germ-free mutant animal models expressed significantly higher levels of thymic stromal lymphopoietin, a major proinflammatory cytokine (and MC mediator) released by disrupted skin, suggesting roles for microbiota in ameliorating keratinocyte stress signals.[80] Commensal bacterial lipoteichoic acid increases skin MC antimicrobial activity against vaccinia viruses.[81] Healthy lung features microbiota different from those of diseased lung.[82] Microbiota-induced bronchial epithelial thymic stromal lymphopoietin production, in turn, induces MC production of mediators pivotal in asthma development.[68] Diet-influenced shift in murine lung microbiota increases circulating SCFAs and protects against allergic pulmonary inflammation.[83] Bacterial virulence factors such as lipoteichoic acid, lipopolysaccharides, and peptidoglycans stimulate the secretion of IL-1ß, tumor necrosis factor-α, IL-6, and IL-8 by epithelial and other gingival cells including MCs, and then further diffusion of these and other cytokines into gingival connective tissue directly or indirectly stimulates many cells including MCs.[84]

Little is known about how dysfunctional MCs interact with microbiota. Given that microbiotic manipulations can reduce normal MC activation, perhaps some abnormal MCs might be similarly quiesced. MC regulation is crucially dependent on a variety of tyrosine kinases, dominantly Kit but also others, including Lyn.[85] Thus, Lyn dysregulation might have MC-dependent consequences. Indeed, Lyn-deficient mice develop increased microbiota-dependent intestinal inflammation and susceptibility to enteric pathogens.[86]

CONCLUSIONS

Conveying a new understanding that all MC disease features inappropriate MC activation, the new top-level designation *MCAD* encompasses various types of rare mastocytosis and likely prevalent MCAS. The apparent uniqueness in each patient with MCAD of constitutively activating mutational patterns in KIT and other MC regulatory elements likely is the principal driver of not only the specific clinical presentation, and therapeutic response profile, in each patient but also the great heterogeneity across this population. The complex systems biology of microbiota are just beginning to be elucidated, but it is clear that there are innumerable interactions with normal MCs, creating the potential for exponentially more complex interactions with the abnormal MCs of MCAD. Much more research lies ahead.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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