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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