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Mast cell mastery

Our new clinical challenge

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Mast cells have been best known for their role in IgE-mediated allergic reactions. Many physicians have generally considered them less important than eosinophils and about as clinically interesting as basophils. But no longer. New insights require the attention of all physicians. Mast cells are multifunctional immune cells active in multiple non-allergy disease states (Table 1). Primary care and subspecialty physicians need to understand, recognize, and treat mast cells.

Mast cells are understood as sentinels and first responders with the capacity to secrete pre-formed and/or de novo-synthesized mediators. These include proteases and vasoactive mediators plus a broad spectrum of cytokines, chemokines, and growth factors with autocrine, paracrine, and systemic effects. They are widely distributed, including the skin, connective tissue, lining of the gastrointestinal tract, respiratory tract, cardiovascular system, reproductive system, and nervous system. Simplified, they are found at the interface of epithelial tissue and the external environment. They are extremely important in maintaining appropriate physiological and pathological functions, including the regulation of vasodilation, vascular homeostasis, innate and adaptive immune responses, angiogenesis, wound healing, bacterial and parasite elimination, as well as bone growth remodeling and remineralization. They are considered protective. But they are also active in detrimental, non-resolving, pro-inflammatory loops in chronic inflammation, cancer, and autoimmune disease.

Mast cells, of course, have the high-affinity IgE receptor that is so important in allergic disease. But they also have many other receptors important in non-allergic disease. These include pathogen recognition receptors (PRRs), and receptors for inflammatory peptides, complement, IgG antibodies, cytokines, chemokines, and growth factors. This means that mast cells can react to many non-allergy types of stimuli. Multiple triggers exist and are delineated in Table 2.

Mast cells are hematopoietic cells that uniquely differentiate in local tissue niches. This means that they are heterogenous in their content and activity. They can be both pro-inflammatory and anti-inflammatory depending upon the microenvironment. They share a core signature of 128 genes relevant to production of their known mediators. Unlike neutrophils and basophils, mast cells are long-lived. They can proliferate despite being fully differentiated. They can recharge and replenish after stimulation. They have innate immune memory.

Mast cell degranulation results in local and systemic effects including vasodilation, skin rashes, flushing, inflammation and swelling, contraction of smooth muscle, altered peristalsis, dyspepsia, nausea, vomiting, headache, palpitations, depressed mood, bone pain, increased mucus production, and anaphylaxis. For this reason, mast cell-related disease results in multiple, non-specific complaints affecting multiple organ systems.

Mast cell activation syndrome

In 2018, the differential diagnosis for patients with complex, chronic, multi-organ system debilitating disease now includes mast cell activation syndrome (MCAS). These patients are often quite impaired yet can have normal screening laboratory values. Their symptoms can look like allergy and atopic disease, but IgE testing can return as normal. They can have multiple chemical sensitivities, adverse food reactions/aversion, non-specific cognitive concerns, and recurrent anaphylactoid reactions. Their symptoms can wax and wane for no apparent reason. Their condition can be mistaken for a mental health issue such as anorexia, hypochondriasis, anxiety, depression, or conversion disorder. Their pleas for relief can escalate to the point of being misdiagnosed with a personality disorder. These patients are also at risk for multiple very expensive medical evaluations without therapeutic relief.

Symptoms can include the common histamine reactions, such as flushing, itching, hives, diarrhea, and hypotension. Symptoms can also include brain fog, cramping, fatigue, weight loss, enlarged lymph nodes, easy bruising/bleeding, headaches, and body aches. In the worst case scenarios, people can experience angioedema and anaphylaxis. The latter are unmistakable; the former can be misperceived as vague and without a unifying diagnosis.

Internationally accepted consensus statements guide use of the term mast cell activation syndrome. Three criteria exist: 1) the presence of mast cell activation symptoms, 2) the presence of the products of mast cell activation, and 3) symptoms that respond to mast cell-stabilizing agents or agents that modify mast cell mediator production, mediator release, or mediator effects. All three need to be fulfilled to meet the definition. However, numerous practical challenges exist in the measurement and documentation of the products of mast cell activation. Ideally, serum tryptase, histamine, and chromogranin A would be measured in emergency rooms when people present with suspected mast cell activation. For many reasons, this is almost never done. And, ideally, 24-hour refrigerated urine collections for prostaglandin D2, leukotriene E4, 2,3 dinor 11-beta prostaglandin F2 alpha, and n-methylhistamine would be done in outpatient settings. However, the half-lives of these mast cell products are both short and temperature sensitive. Hence, these tests require exquisitely careful chain-of-custody management from the clinic to the receiving hospital to Mayo, Quest Diagnostics, LabCorp, or ARUP Laboratories. Practically speaking, from even hospital laboratories, such testing results in a high prevalence of exceptionally low levels of prostaglandin D2, consistent with impaired sample management.

Regretfully, biopsied tissue from any organ is stained for analysis with agents that do not show mast cells. They are invisible: out of sight means out of mind. Ideally, tissue biopsies in patients suspected of having a mast cell disorder should be tested for CD117 and CD25 by flow cytometry, and morphologic descriptions of the mast cells should also be provided. Finally, testing for the gain-of-function mutation in the transmembrane tyrosine kinase receptor c-KIT D816V should be considered.

Common quality-of-life threatening conditions
Migraine, endometriosis, functional dyspepsia, adverse food reactivity, irritable bowel syndrome, postural tachycardic syndrome (POTS), idiopathic dizziness, chronic fatigue syndrome, sleep disturbances, and obesity.
Chronic pain syndromes
Fibromyalgia, chronic pelvic pain, interstitial cystitis, prostatitis, neuro-immune neuropathic pain, nerve compression pain (e.g. sciatica, carpal tunnel), and temporomandibular joint disorder (TMJ).
Neuro-inflammatory disease
Traumatic brain injury, stroke, multiple sclerosis, and intracerebral hemorrhage.
Neurodegenerative disease
Alzheimer's disease and Parkinson's disease.
Neuropsychiatric disorders
Autism, attention-deficit disorder, depression, post-traumatic stress disorder (PTSD), and schizophrenia.
Fibrotic diseases
Cardiac fibrosis, pulmonary arterial hypertension (PAH), idiopathic pulmonary fibrosis, and myelofibrosis.
Cancer and cancer metastases
Atherosclerosis and coronary artery inflammation
Autoimmune diseases
Crohn's disease, Sjogren's syndrome, rheumatoid arthritis, type 1 diabetes, and Guillain-Barre syndrome.

Table 1. Non-Allergy Mast Cell-Associated Medical Conditions

Patients with MCAS can be understood as falling into one of three categories: 1) primary MCAS with c-KIT-mutated, clonal mast cells are present, 2) secondary MCAS where underlying inflammatory disease but no c-KIT-mutated mast cells are found, and 3) idiopathic MCAS where neither an IgE dependent allergy nor c-KIT-mutated mast cells are detectable. To identify which category applies, a bone marrow biopsy is required.

Cautions and precautions

Mast cell activation symptoms can range from mild to life-threatening. The severity depends upon multiple contextual factors, including genetics, number of mast cells, triggerability of the mast cells, the type of allergen, and the presence of co-morbidities. The potential presence of systemic mastocytosis must be considered. Multiple prescription medications can cause mast cell degranulation (a complete list can be found on the Mastocytosis Society website at https://tmsforacure.org). Triggers can also include medication excipients such as coloring agents, etc. Triggerability means that special precautions need to be taken with all medical procedures, including radiology procedures with and without contrast or dyes. Pre-procedure prophylaxis is described here: https://tmsforacure.org/documents/ER_Protocol.pdf.

Mast cell-related disease results in multiple, non-specific complaints affecting multiple organ systems.

Treatment

The best treatment plans include supportive care, resilience training, and trigger avoidance. With these, medications and supplements can be critical for management. At this time, cure is not possible.

Prescription mast cell-stabilizers include cromolyn, ketotifen, and elmiron. The first two are available via specialized compounding pharmacies at lower cost (cromolyn) or capsules (ketotifen). Mast cell-mediator blockade can include H1 blockers (fexofenadine, loratadine, diphenhydramine, cetirizine, hydroxyzine hydrochloride, low-dose Doxepin), and H2 blockers (nizatidine, famotidine, cimetidine, ranitidine). Proton pump inhibitors can be added. With elevated eiconosaids, use of montelukast can be helpful.

In special circumstances, the tyrosine kinase inhibitor imatinib and the anti-IgE antibody omalizumab may be helpful. In 2017, the FDA approved Midostaurin, a multi-kinase inhibitor with activity against c-KIT, for treatment of aggressive mastocytosis.

Non-prescription mast cell-stabilizers represent fundamental treatments. These include quercetin or the quercetin, rutin, luteolin combination sold as NeuroProtek. Additional stabilizers include buffered vitamin C, r-alpha-lipoic acid, vitamin E, and palmitoylethanolamide (PEA). The latter is of particular interest for its wide applicability to pain-related concerns. Low dose naltrexone (LDN) offers additional anti-inflammatory action as a TLR4 antagonist. The probiotic bacteria *Lactobacillus rhamnosis* and Bifodbacter species can reduce histamine loads. In contrast, the probiotic bacteria *Lactobacillus casei* and *Lactobacillus bulgaricus* can produce histamine.

Many patients benefit from a low histamine diet. Additionally, a short-term low FODMAPs diet may help decrease the symptoms while they are undergoing further workup to remove the main trigger or triggers.

Conclusion

Mast cell mastery represents a new competency for all physicians. Three important dimensions deserved to be highlighted.

First, every physician knows of patients who, despite great effort and expense, and despite having a team of skilled clinicians representing multiple subspecialties, still do not have a unifying diagnosis or a satisfactory therapeutic response. Such patients can trigger symptoms of burnout in time-pressured contexts. Mast cell activation syndrome needs to be considered in all such patients.

Second, nearly every subspecialty addresses diseases where aberrant mast cell activation is a strong component of the pathophysiology. Mast cell activation management may represent an important adjunctive or even primary treatment of such diseases.

Third, mast cell activation diseases can fall into an orphan disease category with no primary or subspecialty group being identified as the go-to experts. Examples include patients without IgE-mediated disease and patients without myeloproliferative disease. In fact, in 2016, the World Health Organization removed mastocytosis from the category of myeloproliferative neoplasms due to the disease's heterogenicity. The bottom line is that without any one subspecialty assuming leadership in mast cell related diseases, all of us need to step up and seek mastery in mast cell management.

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Environmental stressors
Heat, cold, or rapid change in temperature; friction, vibration, or mechanical irritation to skin; pollution, pollen, or toxins; sunlight; or scents and fragrances.
Physical stressors
Illness (viral, bacterial, fungal), surgery, exercise, fatigue, or venomous stings.
Emotional stressors
Emotional, psychological, or spiritual stress.
Pharmaceutical stressors
Many medications, including but not limited to amphotericin B, anesthetics, extromethorphan, opiates, vancomycin, and iodine-based contrast dye).
Dietary stressors
Many foods, especially high histamine foods (leftovers, aged cheese, fermented foods, tomato, soy sauce, chocolate, and more).

Table 2. Mast cell triggers