CentraCare Health
Often Seen, Rarely Recognized: Updates in Ehlers-Danlos Syndrome, Complex Regional Pain Syndrome and Mast Cell Activation Syndrome
September 16, 2017

Mast Cell Activation Disease: Basic Concepts ("MCAS 101")
Lawrence B. Afrin, M.D.
Armonk Integrative Medicine
Armonk, NY

Outline
- What is mast cell activation disease (MCAD)?
- What we've long known:
  - Allergic diseases
  - Mastocytosis
  - What's new:
    - Mast cell activation syndrome (MCAS)
- General Clinical Theme
  - Allergy ± Inflammation
  - MC Neoplasia ± Allergy
  - Inflammation ± Allergy (± Aberrant Growth?)

Allergic Diseases
- Allergy, asthma, angioedema, urticaria, anaphylaxis
- 2013: 700 million suffer allergic diseases worldwide
- 10% of preschoolers worldwide now have food allergies
- Steadily increasing incidence/prevalence across all ages
  - e.g., China (prevalence): 1999: 3.5%; 2009: 7.7%
  - Greatest increases in children < 5 years old
- Allergic diseases are conditioned by a number of genes and influenced by environmental factors
  - Incidence of allergic disease in children if...
    - ...neither parent suffers allergic disease: 5-10%
    - ...only one parent suffers allergic disease: 20-40%
    - ...both parents suffer allergic disease: ≥ 60%
- Relatively little mortality, but significant QoL effects

Mastocytosis: A Long History
- 1869: Urticaria pigmentosa (UP) first described
- 1877: First description of the mastcell
- 1885: UP linked with mastzellen
- 1933: Suggestion of linkage with internal dz
- 1939: MC heparin identified
- 1949: Definitive linkage with systemic dz
- 1953: MC histamine identified
- 1957: MC tryptase identified
- 1988: Travis classification
- 1991: First conception "MCAS" might exist
- 1995: KIT activating mutation D816V identified
- 2008: Unique flow cytometric signature found
  - CD117 + (CD25 and/or CD56)
- 2001: WHO classification and imatinib
- MC neoplasia is morbid only in rare, aggressive forms; MC activation is what causes symptoms

Learning Objectives & Disclaimers
- Learning Objectives
- Understand emerging concepts regarding mast cell activation disease (MCAD) including:
  - Key aspects of normal mast cell biology
  - Key distinctions between MCAD subtypes, principally mastocytosis and mast cell activation syndrome (MCAS)
  - The scope of clinical presentation of MCAS
  - Basic principles of diagnosis and treatment of MCAS
- Conflicts of Interest
- None

The Spectrum of Mast Cell Disease
We've Long Known
MCAD: A Brief History

- 1991: 1st published hypothesis that MCAS ought to exist
- 2007: 1st case reports of MCAS
- Some with KIT-D816V, some without
- 2007: 1st study showing other KIT mutations in most MCAS (Bonn)
- 2008: Non-KIT mast cell regulatory gene mutations found in SM
- 2010: 2nd study showing KIT mutations in most MCAS (Bonn)
- KIT-D816V rare
- Few mutations in controls
- 2010: Proposal of “MCAD” (Harvard, Vienna, NIH)
- Includes 1st proposal for MCAS diagnostic criteria
- 2011: Alternative proposal for MCAS diagnostic criteria (Bonn, MUSC)
- 2012: Revisited (Vienna et al.) “consensus” proposal for MCAS dx criteria
- Still many problems
- 2016: Revised WHO diagnostic criteria for SM
- Mastocytosis now separate from the myeloproliferative neoplasms (MPNs)
- “Smoldering SM” added; “SM-AHNMD” shortened to “SM-AHN”
- No statement regarding MCAS

MCAD: Emerging Understanding

Normal mast cell biology

- Hematopoietic origin, brief circulation
- Normally 0.05% of marrow nucleated cells
- Typically < 2% even in systemic mastocytosis
- Unique flow cytometric signature (incl. CD173, CD25/2+)
- Maturation completed in all vascularized tissues
- Especially abundant beneath environmentally exposed mucosal/epithelial surfaces and adjacent to blood and lymphatic vessels and nerves, permitting sentinel function
- Relatively immobile once localized in peripheral tissue
- Lifespan typically several months to a few years

Normal mast cell biology

- Functions (when appropriately stimulated):
  - Synthesize active substances
    - Some stored in granules of highly heterogeneous content
  - Release various mediators upon various triggerings
  - Phagocytose particulate material including bacteria, erythrocytes, schistosomes, metals, etc.
  - KIT stem cell factor receptor and tyrosine kinase (on 4q11-12) is expressed at high levels on the mastocyte surface
  - Critical for many mast cell functions including survival, differentiation, chemotaxis, and activation

Normal mast cell biology
- Capable of synthesizing and releasing many mediators
- Many expressible at very high levels
- Some stored in fully active form in electron-dense secretory granules, tightly packaged with serglycin proteoglycans
- A small sample:
  - Histamine
  - Chymase
  - Cathepsin G
  - Tryptase
  - EGF
  - IFN
  - IL-6
  - CXCL8
  - CCL4
  - Glucuronidase
  - Chondroitin
  - Prostaglandin
  - Serotonin
  - Histamine

Criteria for Systemic Mastocytosis
- **WHO '16**: Indol. SM, smold. SM, SM-AHN, aggressive SM, MC leukemia
- 1 major + 1 minor, or 3 μ minor criteria
- Only major criterion: "Multifocal, dense infiltrates of mast cells consisting of 15 or more mast cells in aggregates detected in sections of bone marrow and/or other extracutaneous organs, confirmed by tryptase immunohistochemistry or other special stains"
- 4 minor criteria:
  - More than 25% of MCs in biopsy sections or bone marrow aspirate smears showing spindle shape or atypical morphology
  - Expression of CD123 and/or CD5 by marrow, blood, or extracutaneous organs
  - Kit exon 8 mutation in bone marrow, blood, or other extracutaneous organs
  - Different Kit mutations → different phenotypes
  - D816V: MC clusters, spindle shape, expression of CD123, histamine, 5HT, etc.
  - Extrathoracic domain: Kit activation
  - Serum total tryptase (μg of MC protein) persistently > 20 ng/ml

The Problem
- It's Chronic Fatigue Syndrome!
- It's POYS!
- It's Fibromyalgia!
- It's Refractory GERD!
- It's Just Old Age!
- It's Granuloma Annulare, or Chronic Inflammatory Demyelinating Polyneuropathy, or... or... or...

Proposed Criteria for MCAS
- (Self-described) "consensus" proposal (2012, tweaked from 2010)
- Problem: Methods by which "consensus" was obtained
  - History consistent with chronic and/or recurrent aberrant mast cell mediator release
  - Problem: Few symptoms listed in proposal (e.g., flushing)
  - Not SM and no better-fitting disease
  - Rise in tryptase (within 4h of flare) of >20% + 2 ng/ml over asymptomatic baseline
  - Problem: establishing "asymptomatic" baseline
  - Problem: getting blood for tryptase level drawn within 4h of flare
  - Problem: allows levels well within normal range to signify disease
  - Problem: no clear data whether this distinguishes ID, CR, or CRD
  - Problem: the only published supporting (?) data weren't published 'til 'ry
  - Problem: the formula keeps getting re-published (NEJM, JACI, etc.) as if it's clearly proven/validated
  - Response to mast cell-targeted therapy
  - Problem: requires therapy prior to diagnosis
  - Problem: should diagnosis of this very heterogeneous disease be ruled out if 1 or 2 lines of empiric therapy fail?

What to do when it behaves like mast cell disease but isn’t just allergy or mastocytosis: Consider mast cell activation syndrome

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*Note: The text is a sampling of information from various sources, focusing on mast cell biology and related conditions.*
Proposed Criteria for MCAS
- Alternative proposal (2011; structure similar to WHO criteria for SM):
  - Major criteria:
    - Multifocal or disseminated disease infiltrates of mast cells in bone marrow biopsies and/or sections of other extracutaneous organs (e.g., gastrointestinal tract
    - Unique constellation of clinical complaints as a result of a pathologically increased mast cell activity (mast cell mediator release syndrome)
  - Minor criteria:
    - Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (>5%) in bone marrow smears or in histologic
    - Detection of genetic changes in mast cells from blood, bone marrow or extracutaneous organs for which an impact on the state of activity of affected mast cells in terms of an increased activity has been proven.
    - Evidence of a pathologically increased release of mast cell mediators (serum tryptase, urinary N-acetylhistamine, plasma heparin, serum chymotrypsin A, or other mast cell-specific mediators (e.g., histamine, prostaglandin D2))
    - Diagnosis made when either both major criteria; or second major criteria
    - At least one minor criterion are met...
    - ...and no other diagnosis that better accounts for the full range and duration of all the symptoms and findings in the history, exam, and lab

MCAS: Emerging Understanding
- Increasing estimates of prevalence
  - 1-17% of the general first-world population?
  - If MCAS dominantly manifests as chronic inflammatory disease (CID), might its prevalence be even higher within populations enriched for CID (e.g., inpatients)?
  - What Portions of These Populations Bear Clonal Mast Cell Disease?

MCAS: Emerging Biology
- May be clonal in most cases...
  - More than 50 mutations (mostly heterozygous, but still functionally dominant) found scattered across all domains of KIT
  - Most patients have multiple KIT (and other) mutations
  - No commercial assays yet for most of these mutations
  - ...but not yet independently confirmed
  - ...thus issue of “non-clonal” vs. “undetermined clonality”
  - Readily available genome/exome sequencing may resolve this soon

MCAS: Do the Biology Math
- MCs produce and release scores of mediators
  - 1 mutation ⇒ aberrant release of N mediators
- Multiple KIT mutations in most MCAS patients?
- Multiple genes mutated in most MCAS patients?
- Each mediator has its own unique array of direct and indirect, local and remote effects

Potential for Multisystem Polymorbidity and Clinical Heterogeneity

MCAS: Presentation
- Typical presentation
  - Age of onset: typically < 30 but unrecognized for decades
  - Usually MULTISYSTEM can affect every system
  - Symptoms often (but not always) “inflammatory”
  - Perplexingly inconstant course:
    - Abnormalities often externally inapparent (“she looks fine!”)
    - Chronic or waxing/waning or episodic (“flares”, “spells”)
    - Different symptoms at different times
  - Often no apparent triggers
  - Mediators:
    - Tryptase (total & mature) usually normal (reflects MC load ⇒ activation)
    - Heparin, CGA, FGD, and histamine (& metabolites), LTE4 often elevated
    - Many MDs, many dx (often non-specific, idiopathic, “somatic”)
  - Patients commonly cease reporting symptoms – ROS important!


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MCAS: Presentation

- Constitutional
  - Fever, chills, fatigue, sweats, weight ↑ or ↓ or ↑ ↓, pruritus
  - Odd and prolific sensitivities (drugs, foods, environs)
- Eyes
  - Irritation, episodic inability to focus vision, blepharospasm
- Ears
  - Irritation, hearing deficit and/or tinnitus
- Nose
  - Irritation, sores, epistaxis, coryza
- Oral/esophageal
  - Irritation, sores, dysphagia, globus

MCAS: Presentation

- GI
  - Inflammation (any/all luminal segments, solid organs)
  - Refractory GERD, IBS, mild ↑ LFTs common
  - Diarrhea + constipation
  - Queasiness, nausea, vomiting (sometimes "cyclical")
  - Malabsorption common (gen., or selected micronutrients)
- GU
  - Inflammation (any/all luminal segments, solid organs)
    - e.g., "interstitial cystitis"
  - ↓ libido, infertility

MCAS: Presentation

- Cardiovascular
  - Unprovoked presyncope/syncope, labile BP/pulse, palpitations
  - Chest pain: coronaries usually clean, but occ. aggressive CAD
  - Arterial, venous malformations; episodic migratory edema
  - Takotsubo (acute balloon CHF, Kounis (allergic angina) synd.

MCAS: Presentation

- Endocrinologic/metabolic
  - Delayed puberty/menarche, dysmenorrhea
  - Osteopenia/osteoporosis, osteosclerosis
  - Hypo/hyperthyroidism, hyperferritinemia (inflammatory)
  - ↑ or ↓ electrolytes, ↑ lipids (often hypertriglyceridemia)
- Growth/Development
  - Poor healing
  - Cysts, fibrosis, endometriosis, vascular anomalies, cancer
  - Connective tissue weakness (e.g., hypermobile Ehlers-Danlos Syndrome?)
  - Autism spectrum disorders
MCAS: Diagnosis

- Traditional diagnostic paradigm (symptom A + exam finding B + test result C ⇒ suspect diagnosis D) doesn’t work for MCAS
- Instead, need to recognize either of two “metapatterns”:
  - Multiple chronic inflammatory symptoms often unsatisfactorily responsive to standard treatments
  - Definitively diagnosed ailment which doesn’t explain all of the symptoms, findings, and results
- Questionnaires? EMRs?

MCAS: Treatment

- 2017: Largely as for indolent mastocytosis
  - Identify and avoid triggers
  - Inhibit mediator production
  - Inhibit mediator release
  - Block actions of released mediators
  - Cytotoxic and cellular therapy only for aggressive SM, MCL
  - Secondary issues and comorbidities

MCAS: Prognosis

- No epidemiologic studies of prognosis yet
- Present gestalt impression:
  - After the first three years, survival curves parallel the general population (similar to indolent systemic mastocytosis)
  - So, like allergic diseases and ISM, reduced survival is a relatively small problem in MCAS, and instead most suffer reduced QoL (anywhere from mild to severe, variable over time) until the disease is accurately diagnosed and effectively controlled
- Many therapies (targeting many receptors and pathways) found helpful in various MCA/MCAS patients
  - Cytotoxic chemotherapy unlikely to help MCAS
  - Most pts eventually identify a significantly helpful regimen

MCAS: Diagnosis

- Best diagnostic aids:
  - Most physicians’ best friend: a complete history and exam
  - Faith in Occam’s Razor: which scenario is more likely?
    - Multiple diagnoses/problems all independent of each other vs.
    - One diagnosis that’s biologically capable of causing most or all of the findings (i.e., the simplest solution, even if it’s not the most immediately obvious solution)
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MCAD: Perioperative Management

- **PLANNING:** Pre-operative consultation with an MCAD-aware anesthesiologist is highly recommended.
- Identify historical triggers (especially peri-/intra-operative drugs, e.g., local anesthetics, antibiotics) as best as possible so they can be avoided.
- Prepare and maintain a relaxing, comfortable OR environment (decrease triggering stress for the patient).

MCAD: Perioperative Medications

- In general:
  - Intensified perioperative H1/H2 blockers
  - ± benzodiazepines (also addressing MC-surface receptors!)
  - ± steroids
  - ± other supportive drugs (e.g., bronchodilators) prn
  - Epinephrine is always the go-to drug for anaphylaxis
  - Glucagon is the “workaround” for patients on beta blockers.

**TABLE 6.** Most common frequency > 10% clinical manifestation findings in mast cell activation syndrome (MCAS). The denominator for each frequency is the eligible portion of the entire study population (e.g., fatigue, all patients [n = 419], dysenteric only female [n = 29]).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>18.8</td>
<td>Dysenteric</td>
<td>9.9</td>
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<tr>
<td>Pruritus</td>
<td>12.1</td>
<td>Impaired sleep</td>
<td>7.7</td>
</tr>
<tr>
<td>Headache</td>
<td>12.1</td>
<td>Urticaria</td>
<td>7.7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12.1</td>
<td>Rhinitis</td>
<td>7.7</td>
</tr>
<tr>
<td>Tired</td>
<td>12.1</td>
<td>Tinnitus</td>
<td>7.7</td>
</tr>
<tr>
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<td>12.1</td>
<td>Orthostatic symptoms</td>
<td>7.7</td>
</tr>
<tr>
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**TABLE 7.** Most common frequency > 10% clinical manifestation findings in mast cell activation syndrome (MCAS). The denominator for each frequency is the eligible portion of the entire study population (e.g., fatigue, all patients [n = 419], dysenteric only female [n = 29]).

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<td>Headache</td>
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MCAD: What’s next?

- **RESEARCH**
  - Improved diagnostic techniques
  - Early genomic sequencing of isolated mast cells to distinguish primary from secondary disease and identify mutational patterns correlating with various clinical presentations
  - Etiology
  - Environmental? Genetic? Epigenetic? Viral?
  - Therapy
  - Predictive biomarkers
  - Targeted therapies
- **EDUCATION** (providers, payers, patients, grantors)

**MCAD: Other Research Ideas**

- Characterization of Mast Cell Regulatory Gene Mutations in MCAS
- MCAD in Refractory GERD
- MCAD in Asthma
- MCAD in Obesity
- MCAD in Fibromyalgia
- MCAD in Chronic Fatigue Syndrome
- MCAD in Irritable Bowel Syndrome
- MCAD in Ehlers-Danlos Syndrome Type III
- MCAD in Postural Orthostatic Tachycardia Syndrome
- MCAD in Atherosclerotic Vascular Disease
- MCAD in Gulf War Illness, Toxican-Induced Loss of Tolerance
- MCAD as a Significant Modifier in Sickle Cell Disease
- Etc. etc. etc.

**Summary**

| MCAD Diagnostic Class | General Prevalence | Phenotype | Tryptase usually...
<table>
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<tbody>
<tr>
<td>Allergic Diseases</td>
<td>Prevalent</td>
<td>Allergy &amp; Inflammation</td>
<td>Normal</td>
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<td>Mastocytosis</td>
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- Tryptase dominantly reflects total body MC load, not activation state
- MCAD symptoms usually from MC activation, not load
- Most MCAD patients...
  - ...have normal survival, making disease control even more important (QOL)
  - ...can eventually find significantly helpful therapy once diagnosed
- Challenges:
  - Heterogeneity (mucosal origin?)
  - No biomarkers yet to predict helpful therapy
  - Education of patients, providers, payers, regulators, grantors, pharma, etc. etc.

**Questions?**