MAST CELL ACTIVATION SYNDROME

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First Signs....

- Since birth... rash, pain, severe allergic reactions
- Negative “allergy tests” to foods
- Also with fatigue, pain, rhinitis, asthma
- Symptoms controlled with diet (6 foods) and environment modifications
Toddler with rashes, colic, asthma, anaphylaxis

- 10 allergists, 4 gastroenterologists, 4 orthopedists, 3 geneticists, 2 rheumatologists, 2 endocrinologists, 2 nutritionists, 2 physical therapists, a cardiologist, neurologist, and pulmonologist (2008 -2011)
- “My son's "complex case" often leaves doctors bewildered or in disbelief, Only recently have we stumbled upon a doctor who is open minded and dedicated to helping us find answers”.
Was fine until...

- 19 year old student athlete with longstanding “allergies”
- Last November, suffered a “stomach bug”
- Started losing weight, even after restricting diet
- Increased vomiting around her menses
- Evaluation and testing with endocrinologists, primary care, gastroenterologists, allergy/immunology specialists- unknown etiology
Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

Matthew J. Hamilton, MD, Jason L. Hornick, MD, PhD, Cem Akin, MD, PhD, Mariana C. Castells, MD, PhD, and Norton J. Greenberger, MD  Boston, Mass

Mast Cell Activation Disorders On the Rise

By Mark L. Fuerst
Reviewed By Miriam K. Anand, MD, FAAAAI, FACAII, Clinical Associate Professor, Arizona College of Osteopathic Medicine, Midwestern University; President, Allergy Associates & Asthma, Tempe, Arizona

Increasing numbers of patients and their physicians are learning that they have mast cell activation (MCA) that is not associated with mastocytosis or with a defined allergic or inflammatory reaction.

Three types of MCA syndromes (MCAS) have been defined, including primary MCAS, secondary MCAS, and idiopathic MCAS. The criteria to define MCAS include:

Typical clinical symptoms
Mast Cells?
Proteins and cells of the Immune System = Defense
Defense Cells & Proteins of the Innate Immune System

“The First Responders” = React with seconds to minutes to danger
Innate receptors have no memory, recognize Invariant Pathogen Associated Molecular Patterns (PAMPs)
Mast Cell Development

(1) Mast Cells: Precursors in the bone marrow
↓
Blood Stream
↓
*Homing to tissues – Gut, Skin, Respiratory Tract
*Granule Production
*Local Survival
Common Mast Cell Triggers
Allergic (IGE) & Non-Allergic (not IGE)
Age of Immune Dysregulated Diseases
20th Century = Increased Burden of Autoimmune and Allergic Diseases

Adapted from Bach, NEJM 2002
Mast Cell Activation Disorders

- Mast Cell (MC) Disorders can affect any organ system, particularly
  - Gastrointestinal tract, Skin, Respiratory Tract
  - MC also have been found in joints, uterus
- Disorders can result from
  - Increased proliferation (mastocytosis, monoclonal MCAS)
  - Increased Activity (nonclonal, overactive Mast Cells)
“Allergies”/Allergic Disorders on the Rise: Rhinitis (Nose Problems), Urticaria (Hives), Angioedema (Swelling), Asthma, Anaphylaxis

Food induced Anaphylaxis

Asthma

Allergic Rhinitis / Sinusitis/ Conjunctivitis

Urticaria / Angioedema
“Allergies”

Find IgE that recognizes harmless ingested, airborne, or contact allergen
Allergic (IGE) Mast Cell Triggers

Detected IGE to:
- Airborne
- Food
- Drugs
- Insects
- Chemicals

Immediate release:
- Granule contents: Histamine, TNF-α, proteases, heparin
  - Sneeze
  - Nasal congestion
  - Itchy, runny nose
  - Watery eyes

Over minutes:
- Lipid mediators: Prostaglandins, Leukotrienes

Over hours:
- Cytokine production: Specifically IL-4, IL-13
  - Mucus production
  - Eosinophil recruitment

Over days:
- bronchoconstriction
Non-IGE mediated Mast Cell Triggers

IGG-Antigen Complexes / Autoimmune

IGG

Physical Triggers
Vibration
Heat
Cold
Solar
Cholinergic

Infections

Medications
- Aspirin
- Opioids
- Antibiotics
- Anesthesia

Coagulation Cascade

Insect Stings
“Allergic” = Allergen-Specific IGE

“Non-Allergic” = Cannot find Allergen-Specific IGE

IMMUNOLOGIC: IgE/FceRI
- foods
- medications
- eg. β-lactam antibiotics
- insect stings/bites
- natural rubber latex
- other

IMMUNOLOGIC: OTHER
- IgG-antigen complexes
- complement system activation
- coagulation system activation

NON-IMMUNOLOGIC
- exercise
- cold air or water
- medications, eg. opioids
- other

CELLS
- MAST CELLS
- BASOPHILS

PREFORMED
- HISTAMINE
- TRYPTASE
- CARBONYLPETIDASE A
- CHYMASE

NEWLY GENERATED
- LEUKOTRIENES
- PROSTAGLANDINS
- PLATELET-ACTIVATING FACTOR

OTHER
- CYTOKINES
- CHEMOKINES

ORGAN SYSTEMS
- SKIN
- RESPIRATORY
- GASTROINTESTINAL
- CARDIOVASCULAR
- CNS

Simons et al, JACI 2009
Anaphylaxis/MCAS

**Skin (80-90% reactions)**
- Hives (urticaria)
- Itch
- Flushing

**Mucosa**
- Itch, swelling – lips, tongue, mouth

**Airway (70% reactions)**
- Throat Tightening, swelling
- Lungs = chest tightness, wheeze,
  can’t take a deep breath

**Genito-Urinary tract (>10% reactions)**
- Uterine Cramping
- Swelling -labia

**Brain (> 20% reactions)**
- Sense of uneasiness
- Headache
- Dizziness
- Confusion
- Tunnel Vision

**Heart, Blood Pressure (10-45 % reactions)**
- Chest Pain
- Fast Heart Rate,
  Palpitations (pounding)
- Weak pulse
- Dizziness
- Fainting

**Gastrointestinal tract (30-45% reactions)**
- Nausea
- Cramping
- Abdominal Pain
- Vomiting
- Diarrhea

**Joint/Muscle Pain**
Mast cell activation syndrome is easily treated, if it's recognized
Hamilton, Reuters 2013

Patients with mast cell activation syndrome (MCAS) frequently go for years without an accurate diagnosis, but once diagnosed and treated, their response is likely to be "excellent"...
Mast Cell Activation Syndrome (MCAS): a collection of disorders characterized by...

- **Accumulation** of pathological mast cells in potentially any or all organs and tissues

- **Aberrant** release of variable subsets of mast cell mediators, leading to one of more symptoms (suggestive of systemic mast cell degranulation)
Got MCAS?
Diagnosis of Mast Activation Disorders/Syndrome

(1) Signs and Symptoms worrisome for MCAS

(2) Respond to medications that target Mast Cells

(3) Data supporting Mast Cell Activation

(4) Ruled out other syndromes that can cause similar symptoms

(5) Clonal vs Nonclonal Mast Cell Activation Disorders
## Classification of MCAS – Mast Cell Activation Disorders

| Primary | Symptoms Associated with monoclonal mast cell population  
A. Mastocytosis  
B. Monoclonal Mast Cell Activation Syndrome (MMAS) |
|---------|-------------------------------------------------------------------------------------------------|
| Secondary | A. Allergic (IGE mediated) Disorders  
B. Mast Cell activation associated with chronic inflammatory (Primary Immunodeficiency) or Neoplastic disorders  
C. Physical Urticaria (Connective Tissue Disorders?)  
D. Chronic Autoimmune Urticaria |
| Idiopathic | A. Anaphylaxis  
B. Angioedema  
C. Urticaria  
D. MCAS |
Clonal Mast Cell Activation Disorder: Signs and Symptoms

- Mastocytosis
- Monoclonal Mast Cell Activation Disorder
  - (Escribano et al, JACI 124:514)

<table>
<thead>
<tr>
<th>Skin Lesions</th>
<th>90%</th>
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<tbody>
<tr>
<td>Pruritis</td>
<td>82%</td>
</tr>
<tr>
<td>Flushing</td>
<td>56%</td>
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<tr>
<td>Diarrhea</td>
<td>35%</td>
</tr>
<tr>
<td>Abdominal Cramping</td>
<td>30%</td>
</tr>
<tr>
<td>Neuropsychiatric Symptoms</td>
<td>23%</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>23%</td>
</tr>
<tr>
<td>Peptic Symptoms</td>
<td>20%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>18%</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>12%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>8%</td>
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</table>
Non-Clonal Mast Cell Activation Disorder: Signs and Symptoms

<table>
<thead>
<tr>
<th>Abdominal Pain</th>
<th>94%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatographism</td>
<td>89%</td>
</tr>
<tr>
<td>Flushing</td>
<td>89%</td>
</tr>
<tr>
<td>Headache</td>
<td>83%</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>67%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>67%</td>
</tr>
<tr>
<td>Rhinitis (Naso-ocular)</td>
<td>39%</td>
</tr>
<tr>
<td>Asthma</td>
<td>39%</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>17%</td>
</tr>
</tbody>
</table>

Mast cell activation disorder

Hamilton, jaci 128;147
(2) Measuring Mast Cell Activation: Activation Markers, Inflammatory Mediators

**Immediate Release**
Granule contents: Histamine, TNF-α, Proteases, Heparin
Sneezing
Nasal congestion
Itchy, runny nose
Watery eyes

**Over Minutes**
Lipid mediators: Prostaglandins, Leukotrienes
Wheezing
Bronchoconstriction

**Over Hours**
Cytokine production: Specifically IL-4, IL-13
Mucus production
Eosinophil recruitment

**Pathology-** spindle MC, MC aggregates

**Serum Tryptase**

**Serum, Urine Histamine**

**Urine**
Histamine, PGD2, 11-beta PGF2

**Allergens**

**IgE**

**CD2, CD25, CD30**

**FcεRI**

**Serum, Urine**
(3) Response to Treatment: Targeting MC/MC Inflammatory Mediators

**Over Minutes**
- Lipid mediators: Prostaglandins, Leukotrienes
- Wheezing, Bronchoconstriction

**Over Hours**
- Cytokine production: Specifically IL-4, IL-13
- Mucus production
- Eosinophil recruitment

**Immediate Release**
- Granule contents: Histamine, TNF-α, Proteases, Heparin
- Sneezing, Nasal congestion, Itchy, runny nose, Watery eyes

**Histamine Blockers, Tricyclic Agents**

**Anti-IGE mAb**
- IgE

**Corticosteroids**
- MC stabilizers

**Leukotriene Blockade**

**TCM** = Traditional Chinese Herbal Medicine
Inherited Connective Tissue Disorders
Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders

Castori, 2012

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Inheritance</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>AD</td>
<td>COL5A1, COL5A2</td>
</tr>
<tr>
<td>Skin extensibility, Jt hypermobility</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>Hypermobility/JHS</td>
<td>AD???</td>
<td>Mostly unknown</td>
</tr>
<tr>
<td>Vascular</td>
<td>AD</td>
<td>COL3A1</td>
</tr>
<tr>
<td>Kypho-scoliotic</td>
<td>AR</td>
<td>PLOD1</td>
</tr>
<tr>
<td>Arthrochalasia</td>
<td>AD</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td>Dermatosparaxis</td>
<td>AR</td>
<td>ADAMTS2</td>
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- Group of inherited connective tissue disorders caused by defect in collagen synthesis, structural proteins or proteins/enzymes involved with collagen 1 biogenesis
- EDS subtypes can be diagnosed clinically or genetically
Of the Six Ehlers Danlos Subtypes, Joint Hypermobility Syndrome is the Most Common
EDS- Hypermobility Syndrome = a hereditary condition with predominant rheumatologic manifestations...

It is now emerging as a multi-systemic disorder with widespread manifestations...

Castori, Dermatology 2012
EDS- Hypermobility Syndrome = a hereditary condition, with widespread, multi-systemic disorders.

Adapted from Castori, Dermatology 2012
## EDS- Hypermobility Syndrome & MCAS

### Subtype

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- All patients had EDS-HJS confirmed by a geneticist, physiatrist or rheumatologist
- 6 adults, 31 to 53 years of age
- 3 children, 5 to 9 years
- 67% female (6 patients)
EDS-JHT: Meeting the Proposed Criteria for MCAS Diagnosis?

1) Episodic Symptoms Consistent with Mast Cell (MC) Activation
   - 9 of 9 patients = skin, GI, CV, respiratory

2) Response to therapy – decrease in frequency, severity or resolution of symptoms with anti-MC mediator therapies or MC stabilizers
   - All 9 patients needed at least 2 classes of anti-MC therapies to control symptoms, and
   - 7 of 9 required rescue B-agonist therapy for acute respiratory or CV distress (albuterol, epinephrine)
Case Series: Meeting the Proposed Criteria for MCAS Diagnosis?

- (3) Evidence of an increase in validated urinary or serum markers of MC activation
  - In NY state, only serum tryptase and 24 hr urine histamine are available, all 9 patients had serum tryptase < 10 IU/ml
  
  Decreased likelihood MMAS, SM or MCL by bone marrow MC aggregates diminishes significantly in those with tryptase < 20 ng/mL (Akin et al, 2011)

- 24 hour urine collection to measure prostaglandin D2 (not available in NY state)
Case Series: Meeting the Proposed Criteria for MCAS Diagnosis?

(4) Rule out Primary and Secondary Causes of MC activation, established clinical entities that trigger or mimic MC activation
• Patients often undergo multiple medical evaluations by different physicians without a definitive diagnosis.
EDS-JHS patients = Secondary MCAS

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<td><strong>C. Physical Urticarias/Systemic Hypersensitivity Reactions = Inherited Connective Tissue Disorders</strong></td>
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<td>D. Chronic Autoimmune Urticaria</td>
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<th>Idiopathic</th>
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</tr>
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<td>C. Urticaria</td>
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<td>D. MCAS</td>
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Mast Cells and the Mucosa

- T cell
- C5a, C3a
- FcγR
- Tolerance breakdown

- NGF
- Serotonin
- Dopamine
- Proteases
- Chymase
- Tryptase
- Chemokines
- MIP1α
- Lymphotactin
- TNF
- Histamine
- Leukotriene
- Prostaglandin

- Connective tissue proliferation and remodelling
- Neutrophil homing, activation
- Vascular adhesion, permeability

- Cytokines
  - IL-4, IL-5, IL-6, IL-10, IL-13, IL-16
Why the delay in diagnosis?

Allergic disease now cause problems of increased complexity and commonly involves several organ systems, so patients are often referred to a succession of different specialists, resulting in confusion.
Anaphylaxis/MCAS - Signs & Symptoms

**Skin (80-90% reactions)**
- Hives (urticaria)
- Itch
- Flushing

**Mucosa**
- Itch, swelling – lips, tongue, mouth

**Airway (70% reactions)**
- Throat Tightening, swelling
- Lungs = chest tightness, wheeze,
  can’t take a deep breath

**Joint/Muscle Pain**

**Brain (> 20% reactions)**
- Sense of uneasiness
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- Nausea
- Cramping
- Abdominal Pain
- Vomiting
- Diarrhea

**Genito-Urinary tract (>10% reactions)**
- Uterine Cramping
- Swelling -labia
Do you have Signs or Symptoms of MCAS?

- **Skin Lesions** (skin biopsy!!!)
- **Liver/Spleen**
  - Elevated Tryptase
  - Abnormal CBC
  - Blood Chemistry
- **NO Skin Lesions**
- **Alternative Diagnosis**
  - **Bone Marrow Biopsy**
- **Clinical Monitoring**
  - every 6-12 Months
  - Tryptase, PGD
  - CBC with Diff
- **Systemic Mastocytosis**
  - WHO classification
THANK YOU!

Xiu-Min Li, MD
William Reed, R-PAC
Office Staff of Comprehensive Allergy & Asthma Care and Mast Cell Center of New York