Mast Cell Disorders

Brian P. Peppers, DO, PhD

January 26, 2018

Osteopathic Recognition Allergy and Immunology Fellowship
University Hospitals Cleveland Medical Center

Cleveland Academy of Osteopathic Medicine
Allergy and Immunology Section
Outline

• Brief History of Mast Cells
• Development of Mast Cells
• Histology of Mast Cells
• Natural Role and Pathophysiology of the Mast Cell
• Disorders of the Mast Cell
• Summary
Brief History of Mast Cells

500 Millions years ago: Mast cells are theorized to have joined with simple eukaryotic organisms.

1842: First described by Paul Ehrlich in his 1878 doctoral thesis on the basis of their unique staining characteristics and large granules.

Originally, believed that the granules existed to nourish the surrounding tissue, and he named them "Mastzellen" (from the German: Mast, "fattening" as of animals).
Brief History of Mast Cells

• 500 Millions years ago: Mast cells are theorized to have joined with simple eukaryotic organisms\(^1\)
Brief History of Mast Cells

• 500 Millions years ago: Mast cells are theorized to have joined with simple eukaryotic organisms\(^1\)

• 1878: First described by Paul Ehrlich in his doctoral thesis on the basis of their unique staining characteristics and large granules\(^2\)

• Originally, believed that the granules existed to nourish the surrounding tissue, and he named them "Mastzellen" (from the German: Mast, "fattening" as of animals).

Actual Thesis June 17, 1878

Paul Ehrlich, “Beiträge zur Theorie und Praxis der Histologischen Färbung”,
Doctoral Thesis, University of Leipzig June 17, 1878
(“Contributions to the theory and practice of the histological coloring”)

Beiträge zur Theorie und Praxis der histologischen Färbung.

ingegangen 17. Juni 1878.

Abschrift

von dem im Besitz der Medizinischen Fakultät der Universität Leipzig befindlichen Original.
Development of Mast Cells

• Mast cells are traditionally difficult to capture and culture in humans.
  – This is secondary to their low numbers in the blood and contamination with other cells in the marrow.

• Mast cells are thought to originate from bone marrow precursors expressing the CD34 molecule.²,³

• Mast cell circulates in an immature form, only maturing once in a tissue site.

• The site an immature mast cell settles in probably determines its precise characteristics.

Mast Cell FcεRI and c-KIT
Mast Cell FcεRI and c-KIT

Allergen

Fc RI

Degranulation/
Allergic Reaction

Anaphylactic verse
Piece-meal Degran.

CD117 or c-KIT
Mast Cell FcεRI and c-KIT

Growth, differentiation, survival and chemotaxis
Electron microscopy of a Human Skin Mast Cell

Electron microscopy of Granules
Left (B): Scrolls
Middle (C): Grates
Right (D): Lattices

Mast cell types

• One type contains the neutral proteases, tryptase and chymotryptic proteinase, and is termed the TC mast cell or MC\textsubscript{TC}.

• The second type contains only tryptase and is termed the T mast cell or MC\textsubscript{T}. 


# Mast Cell Type and Distribution

<table>
<thead>
<tr>
<th>Characteristics of Human Mast Cell Subsets</th>
<th>MC(T)</th>
<th>MC(TC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral Protease</td>
<td>Tryptase</td>
<td>Tryptase, Chymase, Carboxypeptidase, Cathepsin G</td>
</tr>
<tr>
<td>Granule Structure</td>
<td>Scrolls</td>
<td>Lattice/grating</td>
</tr>
<tr>
<td>T Cell Dependence</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Inhibited by NaCromoglycate</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution %</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Less Than 1</td>
</tr>
<tr>
<td>Alveolar Tissue</td>
<td>93</td>
</tr>
<tr>
<td>Nasal Mucosa</td>
<td>66</td>
</tr>
<tr>
<td>Tonsils</td>
<td>40</td>
</tr>
<tr>
<td>Small Intestine</td>
<td></td>
</tr>
<tr>
<td>Mucosa</td>
<td>81</td>
</tr>
<tr>
<td>submucosa</td>
<td>23</td>
</tr>
</tbody>
</table>

# Mast Cell Type and Function

<table>
<thead>
<tr>
<th>Characteristics of Human Mast Cell Subsets</th>
<th>MC(T)</th>
<th>MC(TC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated by Antigen</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Activated by Substance P</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Responds to C5a</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Responds to PAF</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Responds to Opioids</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibited by NaCromoglycate</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

# Mast Cell Type and Function

<table>
<thead>
<tr>
<th>Characteristics of Human Mast Cell Subsets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Activated by Antigen</td>
</tr>
<tr>
<td>Activated by Substance P</td>
</tr>
<tr>
<td>Responds to C5a</td>
</tr>
<tr>
<td>Responds to PAF</td>
</tr>
<tr>
<td>Responds to Opioids</td>
</tr>
<tr>
<td>Inhibited by NaCromoglycate</td>
</tr>
</tbody>
</table>

## Characteristics of Human Mast Cell Subsets

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MC(T)</th>
<th>MC(TC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Less Than 1</td>
<td>99+</td>
</tr>
<tr>
<td>Alveolar Tissue</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>Nasal Mucosa</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>Tonsils</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Small Intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosa</td>
<td>81</td>
<td>19</td>
</tr>
<tr>
<td>Submucosa</td>
<td>23</td>
<td>77</td>
</tr>
</tbody>
</table>

Clinical signs and symptoms of mast cell stimulation

<table>
<thead>
<tr>
<th>Constitutional:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue, malaise</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dermatological:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria pigmentosa, pruritus, flushing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ophthalmologic:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritation, conjunctivitis, dry eyes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Otologic, oropharyngeal:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear/nose/throat inflammation, distorted taste, ulcers, sores, rhinitis, and sinusitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiopulmonary:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper/Hypotension, chest discomfort, faintness, syncope, dyspnea (low grade – often), wheezing, URI, bronchitis, pneumonia, and anaphylaxis (with or without shock)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal discomfort, nausea/vomiting/diarrhea, malabsorption, ulcers, GERD, IBS, Food and drug intolerance, organomegaly (spleen, liver)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone and muscle pain, osteopenia/osteoporosis/osteosclerosis, joint laxity/mobility, fibromyalgia in past medical history</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurologic:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache, peripheral neuropathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunologic:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (II-IV) hypersensitivity reactions, impaired wound healing, increased risk of: infections/malignancy/autoimmune</td>
</tr>
</tbody>
</table>

---

List of Mast Cell Disorders

Cutaneous Mastocytosis
- Urticaria Pigmentosa (UP)/Maculopapular Cutaneous mastocytosis (MPCM)
- Telangiectasia macularis eruption perstans (TMEP)
- Diffuse cutaneous mastocytosis
- Solitary mastocytoma of skin

Extracutanenous Mastocytoma

Systemic Mastocytosis (SM)
- Indolent, systemic, aggressive systemic
- Mast Cell Leukemia
- Mast Cell Sarcoma

Mast Cell Activation syndrome

Vibratory Urticaria

**Urticaria Pigmentosa**

- Urticaria pigmentosa occurs in both children and adults
  - Common for spontaneous remission (~50% of children by adulthood)
  - Children may have bullous eruptions with hemorrhage
  - Present in >90% of individuals with Indolent SM
  - Present in <50% of individuals with Systemic and severe or aggressive SM.
  - Mild irritation or stimulus can cause urticaria
    - (Darier’s sign)
  - Diagnosis is confirmed by skin histopathology

---

Urticaria Pigmentosa

Left: UP in children, small and discrete
But can also have less discrete boarders and larger

Right: Close up of UP lesions

Diffuse Cutaneous Pigmentosa

- Normally occurs before the age of 3
- May have bullous eruptions with hemorrhage
- Skin is often thickened
- Biopsy shows diffuse mast cell infiltrates in the skin

Left: Diffuse CP
Right: Bullous eruptions
With hemorrhage

Telangiectasia macularis eruption perstans (TMEP)

• Adults
• 2-6mm red macule with tan brown background
• Seen in <1% of individuals with mastocytosis
• Pruritus and blistering not commonly associated with TMEP
  – May become edematous
  – Originally described as a blanching macule\(^{12}\)
• Diascopy test

Systemic Mastocytosis

- Slight Female: male ratio (1:1 to 3:1)
- Prevalence is estimated at 20,000-30,000 (in US)
- All ethnic background susceptible, but higher in Caucasians.
- Indolent SM is the most common

Diagnostic Criteria for Systemic Mastocytosis (SM)

If at least 1 major and 1 minor, or at least 3 minor criteria, are met, the diagnosis of Systemic Mastocytosis (SM) can be established.

Major Criteria: Multifocal, dense infiltrates (>15 mast cells in aggregate) of mast cells in bone marrow and/or other extracutaneous organ(s) and confirmed by tryptase or other special stains.

Minor Criteria:
• a) Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (> 25%)
• b) C-kit mutation at codon 816 in extracutaneous organ(s). (Activating mutations at codon 816; in most cases, c-kit D816V)
• c) Mast cells in bone marrow express CD117 with CD2 and/or CD25
• d) Serum total tryptase > 20 ng/mL (does not count in patients who have associated hematologic clonal non-mast cell lineage disease-type disease)

Gain of Function Mutation of D816V

CD117 = Is a Type III Tyrosine Kinase
1) WT gene: Electrostatic repulsion forces keep cytoplasmic “A-loop” away from each other; turned off.
Gain of Function Mutation of D816V

CD117 = Is A Type III Tyrosine Kinase

1) WT gene: Electrostatic repulsion forces keep cytoplasmic “A-loop” away from each other; turned off.

2) D816V: Decreased electrostatic repulsion “A-loop” in D816V mutation

## Indolent, Systemic (AHNMD), and Aggressive SM

<table>
<thead>
<tr>
<th>Diagnosis of SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>If at least 1 major and 1 one minor, or at least 3 minor criteria, are met, the diagnosis of Systemic Mastocytosis (SM) can be established.</td>
</tr>
</tbody>
</table>

### Major Criteria:
Multifocal, dense infiltrates (>15 mast cells in aggregate) of mast cells in bone marrow and/or other extracutaneous organ(s) and confirmed by tryptase or other special stains.

### Minor Criteria:
- a) Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (> 25%)
- b) C-kit mutation at codon 816 in extracutaneous organ(s)
- c) Mast cells in bone marrow express CD117 with CD2 and/or CD25
- d) Serum total tryptase > 20 ng/mL (does not count in patients who have associated hematologic clonal non-mast cell lineage disease-type disease)

---

### B Findings

1. Bone Marrow biopsy >30% infiltration by mast cells and/or Serum total tyrptase >200ng/mL
2. Signs of non-mast cell dysplasia or myeloproliferation (must not meet neoplasm criteria)
3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy

### C Findings

1. No mast cell malignancy with bone marrow dysfunction seen as cytopenias
2. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension
3. Skeletal involvement with large osteolytic lesions and/or pathologic fractures
4. Palpable splenomegaly with hypersplenisms (overactive spleen)
5. Malabsorption with weight loss caused by gastrointestinal mast cell infiltrates

---

### Indolent: No C-findings

### Smoldering: 2 or more B Findings

### SM-AHNMD(AHN): SM with MDS, MPS, AML, plasma cell myeloma, etc.

### Aggressive: one or more C Findings

---

Survival Rates for SM

Expect US survival: Blue line; Observed survival rate for: Indolent (Red), AHNMD (Yellow), Aggressive (Green), Mast Cell Leukemia (~6 months, Purple)

# Treatment for Symptom Control

<table>
<thead>
<tr>
<th>Pharmacologic Therapies for Symptom Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System</strong></td>
</tr>
<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Cutaneous</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Adominal</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Recurrent Hypotension</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

1) Prednisone 0.5-1mg/kg/d; taper as feasible based on response/tolerance
# Mast Cell Activation Syndrome

## Proposed Diagnosis of Mast Cell Activation Syndrome

<table>
<thead>
<tr>
<th>Major Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Multifocal, or disseminated dense infiltrates (&gt;15 mast cells in aggregate) of mast cells in bone marrow and/or other extracutaneous organ(s) and confirmed by tryptase or other special stains.</td>
</tr>
<tr>
<td>2) Clinical Symptoms of increased Mast Cell activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (&gt; 25%)</td>
</tr>
<tr>
<td>b) C-kit mutation at codon 816 in extracutaneous organ(s)</td>
</tr>
<tr>
<td>c) Mast cells in bone marrow express CD117 with CD2 and/or CD25</td>
</tr>
<tr>
<td>d) Evidence of above-normal levels of MC Mediators</td>
</tr>
<tr>
<td>e) Clinical Response to treatment of MC activation/mediators</td>
</tr>
</tbody>
</table>

## Basic difference:

1) MCAS is unable to meet the full Criteria for SM (ISM)
2) Tryptase <20 ng/mL

**Clinical symptoms with clinical response is the most significant addition**

## Diagnosis of SM

<table>
<thead>
<tr>
<th>Major Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>If at least 1 major and 1 one minor, or at least 3 minor criteria, are met, the diagnosis of Systemic Mastocytosis (SM) can be established.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multifocal, dense infiltrates (&gt;15 mast cells in aggregate) of mast cells in bone marrow and/or other extracutaneous organ(s) and confirmed by tryptase or other special stains.</td>
</tr>
</tbody>
</table>

- a) Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (> 25%) |
- b) C-kit mutation at codon 816 in extracutaneous organ(s) |
- c) Mast cells in bone marrow express CD117 with CD2 and/or CD25 |
- d) Serum total tryptase > 20 ng/mL (does not count in patients who have associated hematologic clonal non-mast cell lineage disease-type disease) |

---

New Mast Cell Disorder?

• Vibratory Urticaria
  – Defect in ADGRE2 gene discovered
    • Epidermal Growth Factor seven transmembrane (TM7) Adhesion G protein-couple receptor
    • Autosomal Dominant
    • Missense Mutation with Gain of Function
      – Thought to destabilized the inhibitory interaction between the Alpha and Beta subunits
      – Cysteine substituted for a tyrosine at AA 492(p.C492Y)
        » Wild Type gene: Stronger Non-covalently bond = Less Mast cell activation

Vibratory Urticaria Missense Variant

Left: Alpha and Beta Subunit non-covalently Associated. Blue bars are normal disulfide Bonds. Red bar is the mutation and altered Protein structure.

Right: Blue and Red bars are subjects With mutations. Green = normal gene

A 56 year old female with flushing, chronic fatigue, abdominal pain and diarrhea is being tested for systemic mastocytosis. Based on her current work-up she has? Her lab results are:

- Tryptase of 21ng/mL, In range CBC with diff.
- negative ckit mutation
- negative multifocal dense mast cell aggregates in BM, no abnormal mast cells in
- Mast Cells in BM + for CD117, CD2 and CD25

A) Mast Cell Activation Syndrome  
B) Systemic Mastocytosis  
C) Aggressive SM  
D) Mast Cell Leukemia  
E) Cutaneous Mastocytosis
Review Question 1

A 56 year old female with flushing, chronic fatigue, abdominal pain and diarrhea is being tested for systemic mastocytosis. Based on her current work-up she has? Her lab results are:

- Tryptase of 21ng/mL, In range CBC with diff.
- negative ckit mutation
- negative multifocal dense mast cell aggregates in BM, no abnormal mast cells in
- Mast Cells in BM + for CD117, CD2 and CD25

A) Mast Cell Activation Syndrome
B) **Systemic Mastocytosis**
C) Aggressive SM
D) Mast Cell Leukemia
E) Cutaneous Mastocytosis
A 56 year old female with flushing, chronic fatigue, abdominal pain and diarrhea is being tested for systemic mastocytosis. Based on her current work-up she has? Her lab results are:

- Tryptase of 21ng/mL, ANC: 750, Platelets of 85, remainder of CBC in range
- negative ckit mutation
- negative multifocal dense mast cell aggregates in BM, no abnormal mast cells in BM
- Mast Cells in BM + for CD117, CD2 and CD25

A) Mast Cell Activation Syndrome
B) Systemic Mastocytosis
C) Aggressive SM
D) Mast Cell Leukemia
E) Cutaneous Mastocytosis
A 56 year old female with flushing, chronic fatigue, abdominal pain and diarrhea is being tested for systemic mastocytosis. Based on her current work-up she has? Her lab results are:

- Tryptase of 21ng/mL, ANC: 750, Platelets of 85, remainder of CBC in range
- negative ckit mutation
- negative multifocal dense mast cell aggregates in BM, no abnormal mast cells in BM
- Mast Cells in BM + for CD117, CD2 and CD25

A) Mast Cell Activation Syndrome
B) Systemic Mastocytosis
C) Aggressive SM
D) Mast Cell Leukemia
E) Cutaneous Mastocytosis
A 56 year old female with flushing, chronic fatigue, abdominal pain and diarrhea is being tested for systemic mastocytosis. Based on her current work-up she has? Her lab results are:

- Tryptase of 12ng/mL, CBCd in range
- negative ckit mutation
- negative multifocal dense mast cell aggregates in BM, no abnormal mast cells in BM
- Mast Cells in BM + for CD117, CD2 and CD25

A) Mast Cell Activation Syndrome  
B) Systemic Mastocytosis  
C) Aggressive SM  
D) Mast Cell Leukemia  
E) Cutaneous Mastocytosis
A 56 year old female with flushing, chronic fatigue, abdominal pain and diarrhea is being tested for systemic mastocytosis. Based on her current work-up she has? Her lab results are:

- Tryptase of 12ng/mL, CBCd in range
- negative ckit mutation
- negative multifocal dense mast cell aggregates in BM, no abnormal mast cells in BM
- Mast Cells in BM + for CD117, CD2 and CD25

A) Mast Cell Activation Syndrome
B) Systemic Mastocytosis
C) Aggressive SM
D) Mast Cell Leukemia
E) Cutaneous Mastocytosis
Summary

• Cutaneous Mastocytosis in children seldom have comorbid systemic mastocytosis
• Mast Cell Disorders often present as a combination of vague clinical symptoms
• Indolent systemic Mastocytosis is the most common and least severe
• Aggressive SM and Mast Cell Leukemia are the least common and lowest life expectancy
• Although there are promising new treats in clinical trials, symptom control remains the staple management plan
Acknowledgements

• University Hospitals Cleveland Medical Center and Lake Erie Consortium of Osteopathic Medical Training

• **Fellowship Mentors:**
  – Robert W. Hostoffer, DO, LhD (Program Director)
  – Haig Tcheurekdjian, MD
  – Theodore Sher, MD
  – Devi Jhevari, DO

• Colleagues in the Fellowship
Acknowledgements

• University Hospitals Cleveland Medical Center and Lake Erie Consortium of Osteopathic Medical Training

• Fellowship Mentors:
  – Robert W. Hostoffer, DO, LhD (Program Director)
  – Haig Tcheurekdjian, MD
  – Theodore Sher, MD
  – Devi Jhevari, DO

• Colleagues in the Fellowship

• All of You!!!