What are Mast Cells?

- Mast cells are immune system cells that live in the bone marrow and in body tissues, internal and external, such as the gastrointestinal tract, the lining of the airway and the skin.
- Mast cells are involved in allergic reactions.
- Mast cells have within them small “sacs” surrounded by membranes.

Mast cell granule (sac) which contains mediators

Mast cell (electron micrograph)
The sacs within mast cells (granules) contain many different kinds of substances called mediators, which participate in allergic or other reactions and anaphylaxis.

Those mediators are normally selectively released when there is an allergic or mast cell-based reaction.

These mediators, when released, cause symptoms of mast cell activation.

# Possible Effects of Some Mast Cell Mediators

<table>
<thead>
<tr>
<th>MEDIANOR</th>
<th>POSSIBLE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Flushing, itching, diarrhea, hypotension</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Flushing, bone pain, brain fog, cramping</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Osteoporosis, skin lesions</td>
</tr>
<tr>
<td>Interleukins</td>
<td>Fatigue, weight loss, enlarged lymph nodes</td>
</tr>
<tr>
<td>Heparin</td>
<td>Osteoporosis, problems with clotting/bleeding</td>
</tr>
<tr>
<td>Tumor Necrosis Factor-α</td>
<td>Fatigue, headaches, body aches</td>
</tr>
</tbody>
</table>

Potential Mast Cell Triggers

- Venoms (bee/wasp, jelly fish, snake, spider, fire ant, etc.)
- Food or alcoholic beverages
- Drugs (opioids, NSAIDs, and some local anesthetics)
- Friction, vibration or mechanical irritation
- Emotional, physical, social or environmental stress
- Heat, cold, sudden temperature changes
- Infections (viral, bacterial, or fungal)
Symptoms of Mast Cell Activation
(What Happens When Your Mast Cells Activate?)

- Flushing
- Itching
- Hives
- Angioedema (swelling)
- Nasal itching and congestion
- Wheezing and shortness of breath
- Throat itching and swelling

- Headache and/or brain fog
- Diarrhea, nausea, vomiting, abdominal pain, bloating
- Light-headedness
- Rapid heart rate
- Low blood pressure
- Anaphylaxis

When Does This Become Anaphylaxis?

Anaphylaxis is an acute life-threatening systemic reaction that results from the sudden, rapid, systemic release of mediators.

**MOUTH** itching, swelling of lips and/or tongue
**THROAT*** itching, tightness/closure, hoarseness
**SKIN** itching, hives, redness, swelling
**GUT** vomiting, diarrhea, cramps
**LUNG*** shortness of breath, cough, wheeze
**HEART*** weak pulse, dizziness, passing out

Only a few symptoms may be present; even if anaphylaxis presents with symptomatology from 1 organ system (e.g., hypotension, or as an acute cardiac or respiratory event) epinephrine administration may be indicated. Severity of symptoms can change quickly. *Some symptoms can be life-threatening. Act quickly!*

- AAAAI Anaphylaxis Plan
- TMS Emergency Care Pamphlet

ACTIVATE YOUR ANAPHYLAXIS ACTION PLAN!!!!
Basic Medication Protocol for Mast Cell Diseases

- **H1 antihistamines** - help with itching, abdominal pain, flushing, headaches, brain fog and general mast cell stability, which in turn may reduce multiple symptoms
- **H2 antihistamines** - help with gastrointestinal symptoms and overall mast cell stability
- **Mast cell stabilizers** - help with stomach, intestinal symptoms, and brain fog
- **Leukotriene inhibitors** - help with respiratory symptoms and overall mast cell stability
- **Aspirin therapy** (if tolerated; if prostaglandins are elevated) - helps with flushing, brain fog and bone pain
- **Anti-IgE therapy** (e.g., omalizumab) - helps with asthma, anaphylaxis and overall mast cell stability

1st Generation H1 Antihistamines Include:

- Atarax® (hydroxyzine hydrochloride)
- Benadryl® (diphenhydramine)
- Chlortrimeton® (chlorpheniramine)
- Doxepin®, Sinequan® (doxepin hydrochloride)
- Ketotifen
2nd Generation H1 Antihistamines May Tend to Cause Less Drowsiness, and Include:

Allegra® (fexofenadine)
Claritin® (loratidine)
Clarinex® (desloratidine)
Xyzal® (levocetirixine)
Zyrtec® (cetirizine)
What are Some H2 Antihistamines?

Axid® (nizatadine)
Pepcid® (famotidine)
Tagamet® (cimetidine)
Zantac® (ranitidine) (has been taken off market)
What are Some Mast Cell Stabilizers?

Gastrocrom® (oral cromolyn sodium)

Ketotifen

Bioflavonoids such as quercetin and luteolin

What are Some Leukotriene Inhibitors?

Singulair® (montelukast)
Accolate® (zafirlukast)
Zyflo®/Zyflo CR® (zileuton)
Other Therapies for Mast Cell Disease Patients May Include:

Aspirin Therapy

ASA (Aspirin)- *always initiated under the supervision of a physician*

Anti-IgE Therapy

Xolair® (Omalizumab)
What are Some Proton Pump Inhibitors to Help with GERD (Gastroesophageal Reflux)?

Aciphex® (rabeprazole)
Dexilant® (dexlansoprazole)
Nexium® (esomeprazole)
Prevacid® (lansoprazole)
Prilosec® (omeprazole)
Protonix® (pantoprazole)
Midostaurin (Rydapt®)
Avapritinib (Ayvakit®)
Other D816V KIT inhibitors are currently in clinical trials (e.g., Ripretinib)
Cladribine (2-CdA; 2 chloro-2 deoxyadenosine; Leustatin® Leustat® Litak®)
INF-α2b (Interferon Alpha 2b)
Imatinib (Gleevec®)
Masitinib (Masivet®)
Dasatinib (Sprycel®)
Nilotinib (Tasigna®)
Hydroxyurea (Hydrea®)
Definitions

- **Darier’s sign** - important diagnostic finding of patients with mastocytosis; can be elicited by stroking an *existing* typical mastocytosis skin lesion approximately 5 times with moderate pressure. Within a few minutes, a wheal and flare reaction of the lesion will be seen.

- **Dermatographism** - skin reaction characterized by a wheal and flare response when normal skin, *not affected by skin lesions*, is stroked with a tongue depressor, fingernails or other instrument.

- A **macule** - lesion that is flat and even with the surrounding skin, identified by a change in color compared to the surrounding skin.

- A **papule** - small bump or elevated lesion, up to 1 cm in diameter, containing no visible fluid.

- A **nodule** - growth of abnormal tissue just below the skin.

- **Bulla/bullae** - large blister(s) filled with fluid.

- **Telangiectasia** - a vascular lesion formed by dilatation of a group of small blood vessels.
What are the Diagnostic Criteria for Systemic Mastocytosis?

**Major:**
Clusters of 15 or more mast cells in a site other than the skin

**Minor:**
- Abnormal shape or morphology of mast cells (e.g., spindle shape)
- Expression of abnormal markers on the surface of mast cells, such as CD25 and/or CD2
- The *KIT* D816V or other *KIT* mutations
- Serum Tryptase > 20 ng/mL

1 Major and 1 Minor or 3 Minor criteria are required for the diagnosis


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Mast Cell Aggregates

Bone Marrow Core Sample with CD117 Immunostaining
What is the *KIT* Mutation?

- *KIT* is a growth receptor on surface of mast cells that plays a role in telling the cell whether or not to grow or divide.

- Mutation in *KIT* can cause mast cells to grow abnormally and in greater numbers (proliferation and accumulation).

- The most common mutation that affects patients with systemic mastocytosis is D816V, which we refer to as the *KIT* mutation (there can be other mutations within *KIT* that are not as common).

Spindle-Shaped Mast Cells
D816V KIT Mutation

Affects 95% of patients with systemic mastocytosis

Why is it important to know your KIT status?

Patients with the D816V mutation may be resistant to Gleevec® (imatinib mesylate) and should not take Gleevec® except under the direction of an experienced mast cell disease specialist (usually a hematologist). Knowing your KIT status helps you to determine with your physician which treatments you are eligible for.

Clonal mast cell disease describes a defect or change within the DNA in some of the mast cells in an individual. Those mast cells have abnormal characteristics as a result. The most common example of such a defect in mast cells is the KIT D816V mutation. Other similar KIT mutations are also considered evidence of clonal disease. Non-clonal mast cell disease means there has been no change to the DNA in an individual’s mast cells, such as a KIT mutation.

Abnormal Surface Markers in Systemic Mastocytosis

- CD117 identifies mast cells
- CD2, CD25 & CD30: Lymphocyte surface markers not found on normal mast cells.
- CD stands for cluster of differentiation

Overview: Current Classification of Mast Cell Diseases

- **Cutaneous Mastocytosis (adult and pediatric) (CM)**
  - Maculopapular Cutaneous Mastocytosis (MPCM)/Urticaria Pigmentosa (UP)
    - Monomorphic (primarily adults and small subset of children)
    - Polymorphic (primarily children)
  - Diffuse Cutaneous Mastocytosis (DCM)
  - Cutaneous Mastocytoma

- **Indolent Systemic Mastocytosis (adult and pediatric) (ISM)**
  - Isolated Bone Marrow Mastocytosis (BMM)

- **Smoldering Systemic Mastocytosis (SSM)**

- **Systemic Mastocytosis with an Associated Hematological Neoplasm (SM-AHN)**

- **Aggressive Systemic Mastocytosis (ASM)**

- **Mast Cell Leukemia (MCL)**

- **Mast Cell Sarcoma (MCS)**

- **Mast Cell Activation Syndromes**
  - Mast Cell Activation Syndrome, Monoclonal (MMAS) (Primary)
  - Mast Cell Activation Syndrome, Secondary (MCAS)
  - Mast Cell Activation Syndrome, Idiopathic (MCAS)

- **Hereditary alpha Tryptasemia (HαT)**

*Can also present as Well-Differentiated forms of mastocytosis*
Cutaneous Mastocytosis (CM)

Adult and Pediatric

- Maculopapular Cutaneous Mastocytosis (MPCM)/Urticaria Pigmentosa (UP)
  - Monomorphic (primarily adults and small subset of children)
  - Polymorphic (primarily children)
- Diffuse Cutaneous Mastocytosis (DCM)
- Cutaneous Mastocytoma

Maculopapular Cutaneous Mastocytosis (MPCM)

- Most common lesions seen in children. Good prognosis. 70-80% resolve or improve by early adulthood.

- Serum tryptase generally <20 ng/ml

- Type of lesions in childhood may be predictive of prognosis (monomorphous lesions, all the same size, may persist into adulthood versus polymorphous lesions, of various sizes).

- The majority of adults with MPCM are ultimately diagnosed with SM (usually ISM) after a bone marrow biopsy. Rarely do they retain a true diagnosis of pure cutaneous disease.


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Diffuse Cutaneous Mastocytosis (DCM)

- Children with DCM exhibit generalized redness with thickened skin; skin may appear dark overall.
- Raised lesions may be present in thickened skin with positive dermatographism.
- Large blisters can be triggered by rubbing, scratching, viral infections or teething.
- Bleeding from skin wounds may be the result of local heparin release.
- Serum tryptase levels usually elevated; no systemic organ involvement seen.
- Lesions usually resolve by late adolescence or young adulthood.

Cutaneous Mastocytoma

- Mastocytoma usually presents as a single, elevated brown, red or yellow lesion. Some children may present with more than 1 lesion. *More than three lesions changes the diagnosis to maculopapular cutaneous mastocytosis (MPCM).*

- Blistering over the lesion may be observed.

- Upon stroking the lesion, flushing, reddening of the skin and sweating may occur.

- Serum tryptase levels are usually normal.

- No systemic involvement is found, and mastocytomas usually do not persist into adulthood.

Systemic Mastocytosis and Variants

- **Indolent Systemic Mastocytosis (adult and pediatric) (ISM)**
  - Isolated Bone Marrow Mastocytosis (BMM)
- **Smoldering Systemic Mastocytosis (SSM)**
- **Systemic Mastocytosis with an Associated Hematological Neoplasm (SM-AHN)**
- **Aggressive Systemic Mastocytosis (ASM)**
- **Mast Cell Leukemia (MCL)**
- **Mast Cell Sarcoma (MCS)**

*Can also present as **Well-Differentiated** forms of mastocytosis*
Indolent Systemic Mastocytosis

- Most common category in adults. May or may not present with skin involvement.
- Serum tryptase generally >20 ng/ml
- Good prognosis in most patients; symptomatic treatment
- Also includes:
  - Isolated bone marrow mastocytosis (BMM), which is *ISM with no skin lesions*

Well-Differentiated Systemic Mastocytosis (WDSM)

• May not meet 2008 World Health Organization (WHO) diagnostic criteria for SM
• May be represented in all systemic variants
• Skin lesions present
• MCs with round-shape
• Negative or weak expression of CD25 and CD2 on bone marrow mast cells
• May have serum tryptase levels > or <20 ng/mL
• KIT D816V mutation is infrequent, but other KIT mutations may be present (or other evidence of clonal mast cells)
• WDSM has been reported to show excellent responses to imatinib therapy in those who lack the KIT D816V mutation.

The patient fits the criteria for systemic mastocytosis and also has a secondary hematological or a myeloproliferative neoplasm (MPN) that is not derived from their mast cells.

Examples include: leukemias such as CML/CMML and AML, Polycythemia Vera, Essential Thrombocytosis, Myelofibrosis, and Myelodysplastic Syndrome.
What are “B” Findings?

B-findings: Be aware of changes!

- Big liver +/- big spleen without impairment in function
- +/- enlarged lymph nodes
- Mast cells > 30% of the bone marrow smear
- +/- serum tryptase >200 ng/ml
- Increase in bone marrow cellularity (hypercellular)

What are “C” Findings?

C-findings: Consider Chemotherapy!

- Very low number of cells in the blood (cytopenia)
- “Holes” in the bone (osteolysis) with or without pathologic bone fractures
- Large liver and spleen with abnormal function of these organs
- Extra fluid in the abdomen (ascites)
- Reduced nutrient uptake with weight loss and low blood albumin (a protein)


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Smoldering Systemic Mastocytosis

- Category between Indolent and Aggressive Systemic Mastocytosis

- Patients may begin to exhibit **two or more “B” findings**, but no **“C” findings**, and demonstrate a progression towards more aggressive disease.
Aggressive Systemic Mastocytosis

- Meets WHO mastocytosis criteria for diagnosis of SM
- Mast cells on a bone marrow smear comprising <20% of the bone marrow cells
- No associated hematologic non-mast cell lineage disorder
- May or may not have B-findings but will have 1 or more C-findings (only one C-finding required to meet criteria)

Mast Cell Leukemia

- Prognosis varies with type
- Typical MCL: Presence of mast cells >10% in peripheral blood; 20% or more diffuse infiltration of bone marrow with compact, atypical, immature mast cells.
- Aleukemic MCL: < 10% of peripheral blood white cells are MCs. Usually without skin lesions. Extremely rare. Tryptase levels markedly elevated.

Mast Cell Sarcoma

- Malignant, invasive solid mast cell tumor
- Aggressive course is typically seen
- Rare

Mast Cell Activation Syndrome (MCAS)

• Symptoms of mast cell activation, in two or more organ systems at the same time, can be acute, episodic and recurrent, or chronic and frequent, may present as generalized, systemic symptoms, including anaphylaxis, and can not be explained by any other disease process.

• A rise in mast cell mediators, such as serum tryptase (20% above baseline, plus 2 ng/ml), urinary n-methyl histamine or other histamine metabolites, prostaglandin D₂, or its metabolite, 11β-prostaglandin F₂α or leukotriene E4, or MIAA where available

• A response to mast cell mediator or mast cell stabilizer therapy

Mast Cell Activation Syndromes (adult and pediatric)

- Mast Cell Activation Syndrome, Monoclonal (MMAS) (Primary)
- Mast Cell Activation Syndrome, Secondary (MCAS)
- Mast Cell Activation Syndrome, Idiopathic (MCAS)
Monoclonal Mast Cell Activation Syndrome (MMAS) (Primary)

- If abnormal mast cells are identified, but the patient does not fulfill criteria for SM, it is called **Monoclonal Mast Cell Activation Syndrome**.

- The symptoms of mediator release are treated the same as with other mast cell diseases.
Mast cell activation occurs as an indirect result of another disease or condition.

IgE allergy may be the cause of secondary MCAS. Other causes may include infection, autoimmune or other disease.

Treatment involves therapy for the underlying cause as well as antimediator and mast cell stabilizing therapy.
MCAS, Idiopathic

- Nonclonal disease; cause of disease unknown
- MCAS criteria have been fulfilled.
- All known causes for secondary mast cell activation, such as infection, allergy or autoimmune disease, have been ruled out.
- Treatment is aimed at controlling mast cell mediator release and preventing anaphylaxis.

Hereditary alpha tryptasemia (HαT) is an autosomal dominant genetic trait caused by a duplication, triplication or multiple copies of the alpha-tryptase gene.

If you have elevated tryptase with or without SM, it is important to be tested for HαT.

Not everyone who tests positive for HαT will be symptomatic.

Individuals with this trait have increased basal serum tryptase levels, and may experience symptoms such as:

- itching, hives, flushing
- anaphylaxis
- bloating, GERD, abdominal pain, diarrhea and/or constipation, IBS, difficulty swallowing
- connective tissue symptoms such as hypermobile joints, scoliosis
- tachycardia, unstable blood pressure and dysautonomia

H\(\alpha\)T is a risk factor for severe anaphylaxis and can modify mast cell diseases. The connection between mast cell activation and H\(\alpha\)T has not been clearly defined.

Researchers are working to determine:

1. How does H\(\alpha\)T affect patients who also have mastocytosis or MCAS?
2. Can the increased tryptase cause symptoms without mast cell activation?
3. Can the increased tryptase intensify normal mast cell activation?

How Can I Get Tested and Treated for HαT?

• A serum tryptase level (blood test) can help determine if your basal serum tryptase is over 8 ng/ml. If your serum tryptase is under 8 ng/ml, it is less likely that you have HαT.

• Treatment is symptomatic. The course of HαT is not known at this time. More research is needed into this area.

• Gene by Gene makes a test specific for HαT.

www.niaid.nih.gov/research/hereditary-alpha-tryptasemia-faq
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