

The Mastocytosis Society, Inc. (TMS)

(Changing to The Mast Cell Disease Society, Inc. effective June 30, 2020)

Presents

The Mast Cell Disease Primer

TMS



- Valerie M. Slee, RN, BSN, Chair
- Susan Jennings, PhD, Research Chair
- Jan Hempstead, RN, Vice-Chair, Patient Care Coordination Chair

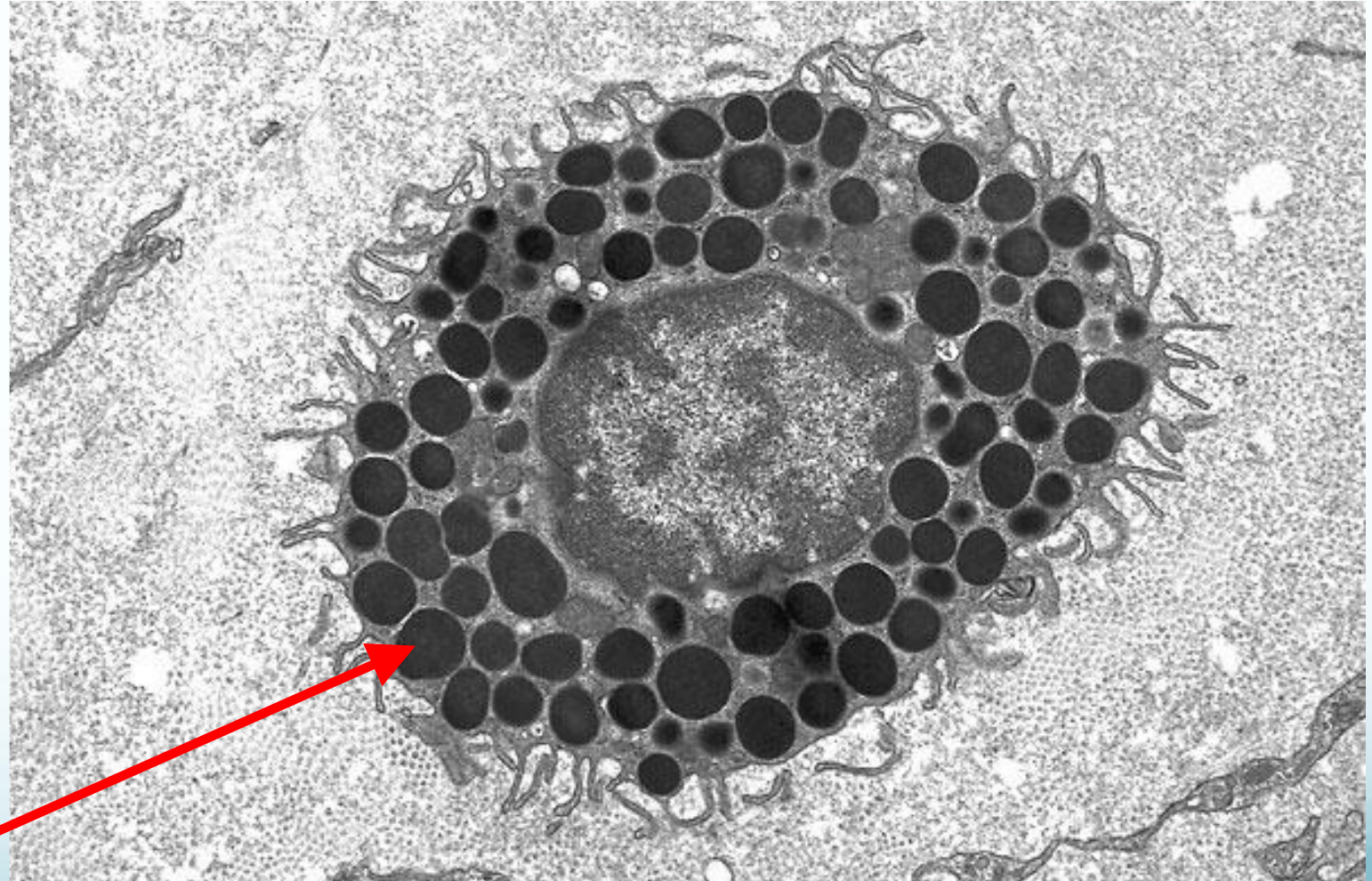
THE MASTOCYTOSIS SOCIETY

Mast Cell Diseases

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)

What are Mediators?

- 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.

Gilfillan AM, et al. Adv Exp Med Biol. 2011;716:2-12.

Possible Effects of Some Mast Cell Mediators

| MEDIATORS | POSSIBLE EFFECTS |
|---------------------------------|---|
| Histamine | Flushing, itching, diarrhea, hypotension |
| Leukotrienes | Shortness of breath |
| Prostaglandins | Flushing, bone pain, brain fog, cramping |
| Tryptase | Osteoporosis, skin lesions |
| Interleukins | Fatigue, weight loss, enlarged lymph nodes |
| Heparin | Osteoporosis, problems with clotting/bleeding |
| Tumor Necrosis Factor- α | Fatigue, headaches, body aches |

Carter MC, et al. Immunol Allergy Clin North Am. 2014;34(1):181-96.

Theoharides TC, et al. N Engl J Med. 2015;373(2):163-72.

Potential Mast Cell Triggers

- Venoms (Wasp, Jelly Fish, etc.)



- Food or alcoholic beverages



- Drugs (opioids, NSAIDs, and some local anesthetics)



- Mechanical irritation



- Emotional or physical stress



- Sudden temperature changes



- Infections (viral or bacterial)



Silva I, et al. Allergol Immunopathol (Madr). 2008 May-Jun;36(3):154-63.

Symptoms of Mast Cell Activation (What Happens When Your Mast Cells Flare?)

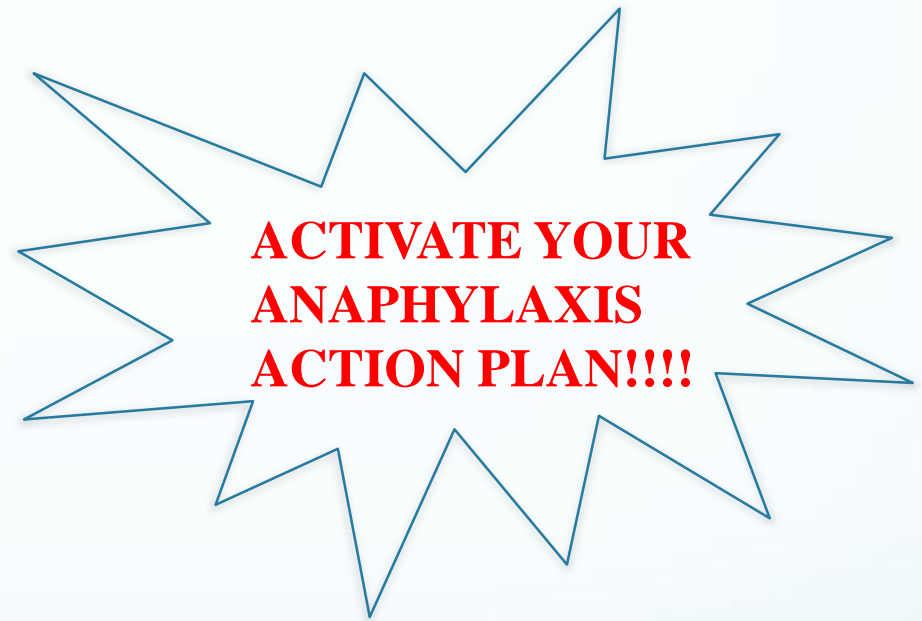
- Flushing
- Itching
- Hives
- Angioedema (swelling)
- Nasal itching and congestion
- Wheezing and shortness of breath
- Throat itching and swelling
- Headache and/or brain fog
- Diarrhea, nausea, vomiting, abdominal pain, bloating
- Light-headedness
- Rapid heart rate
- Low blood pressure
- **Anaphylaxis**

Valent P, et al. Int Arch Allergy Immunol. 2012;157(3):215-25.
Theoharides TC, et al. N Engl J Med. 2015;373(2):163-72.

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 FAST!

- [AAAAI Anaphylaxis Emergency Action Plan](#)
- [TMS Emergency Care Pamphlet](#)

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 reduces all symptoms
- **H2 antihistamines**- help with gastrointestinal symptoms and overall mast cell stability (all symptoms)
- **Mast cell stabilizers**- help with stomach and intestinal symptoms and brain fog
- **Leukotriene inhibitors**- help with respiratory symptoms and overall mast cell stability (all symptoms)
- **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

Theoharides TC, et al. N Engl J Med. 2015;373(2):163-72.

1st Generation H1 Antihistamines include:

Atarax[®] (Hydroxyzine hydrochloride)

Benadryl[®] (Diphenhydramine)

Chlortrimeton[®] (Chlorpheniramine)

Doxepin[®], Sinequan[®] (Doxepin hydrochloride)

2nd Generation H1 Antihistamines may tend to cause less drowsiness, and include:

Allegra[®] (Fexofenadine)

Claritin[®] (Loratidine)

Clarinex[®] (Desloratidine)

Ketotifen (has also been listed as a 1st generation H1 antihistamine in some articles)

Xyzal[®] (Levocetirixine)

Zyrtec[®] (Cetirizine)

What are some H2 Antihistamines?

Axid[®] (Nizatadine)

Pepcid[®] (Famotidine)

Tagamet[®] (Cimetidine)

Zantac[®] (Ranitidine)

What are some mast cell stabilizers?

Gastrocrom[®] (oral cromolyn sodium)

Ketotifen

Bioflavonoids such as quercetin and luteolin

Valent P, et al. Leuk Res. 2001 Jul;25(7):603-25.

Hungness SI, Akin C. Curr Allergy Asthma Rep. 2007 Jul;7(4):248-54.

Weng Z, et al. PloS one. 2012;7(3):e33805.

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 (Anti-IgE therapy)

What are some proton pump inhibitors to help with GERD (gastroesophageal reflux)?

Aciphex[®] (rabeprazole)

Dexilant[®] (Dexlansoprazole)

Nexium[®] (Esomeprazole)

Prevacid[®] (Lansoprazole)

Prilosec[®] (Omeprazole)

Protonix[®] (Pantoprazole)

Some Chemotherapy Drugs for Aggressive Variants of SM

Midostaurin (Rydapt[®])

Other D816V KIT inhibitors are currently in clinical trials
(e.g., Avapritinib and Ripretinib)

Cladribine (2-CdA; 2 chloro-2 deoxyadenosine; Leustatin[®] Leustat[®] Litak[®])

INF- α 2b (Interferon Alpha 2b)

Imatinib (Gleevec[®])

Masitinib (Masivet[®])

Dasatinib (Sprycel[®])

Nilotinib (Tasigna[®])

Hydroxyurea (Hydrea[®])

Valent P, et al. Blood. 2017 Mar 16;129(11):1420-1427.

What Are the Diagnostic Criteria for Systemic Mastocytosis?

Major:

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

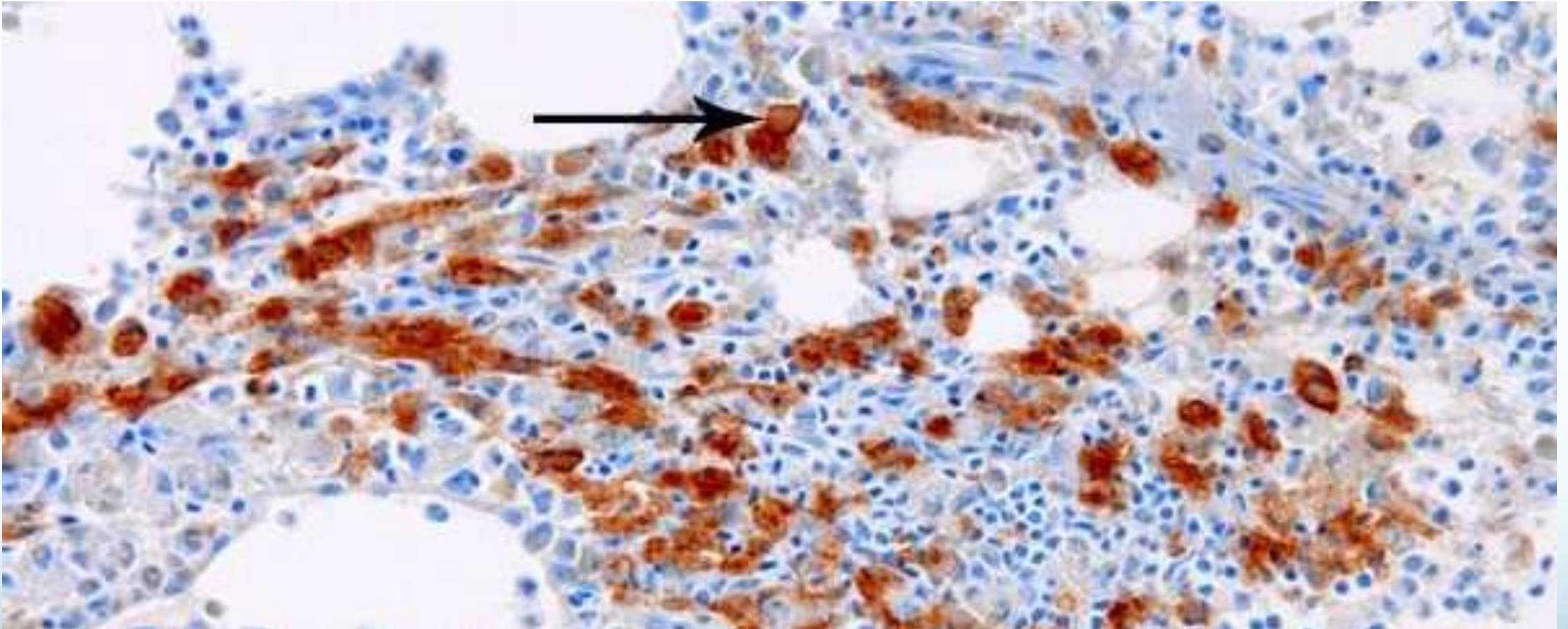
Minor:

- Abnormal shape of mast cells- such as spindle shape
- Expression of abnormal markers on the surface of mast cells such as CD25 and/or CD2 (*note: CD2 is under consideration for removal from the criteria*)
- The *KIT* D816V mutation
- Serum Tryptase > 20 ng/mL

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

Valent P, et al. Eur J Clin Invest. 2007 Jun;37(6):435-53.

Mast Cell Aggregates



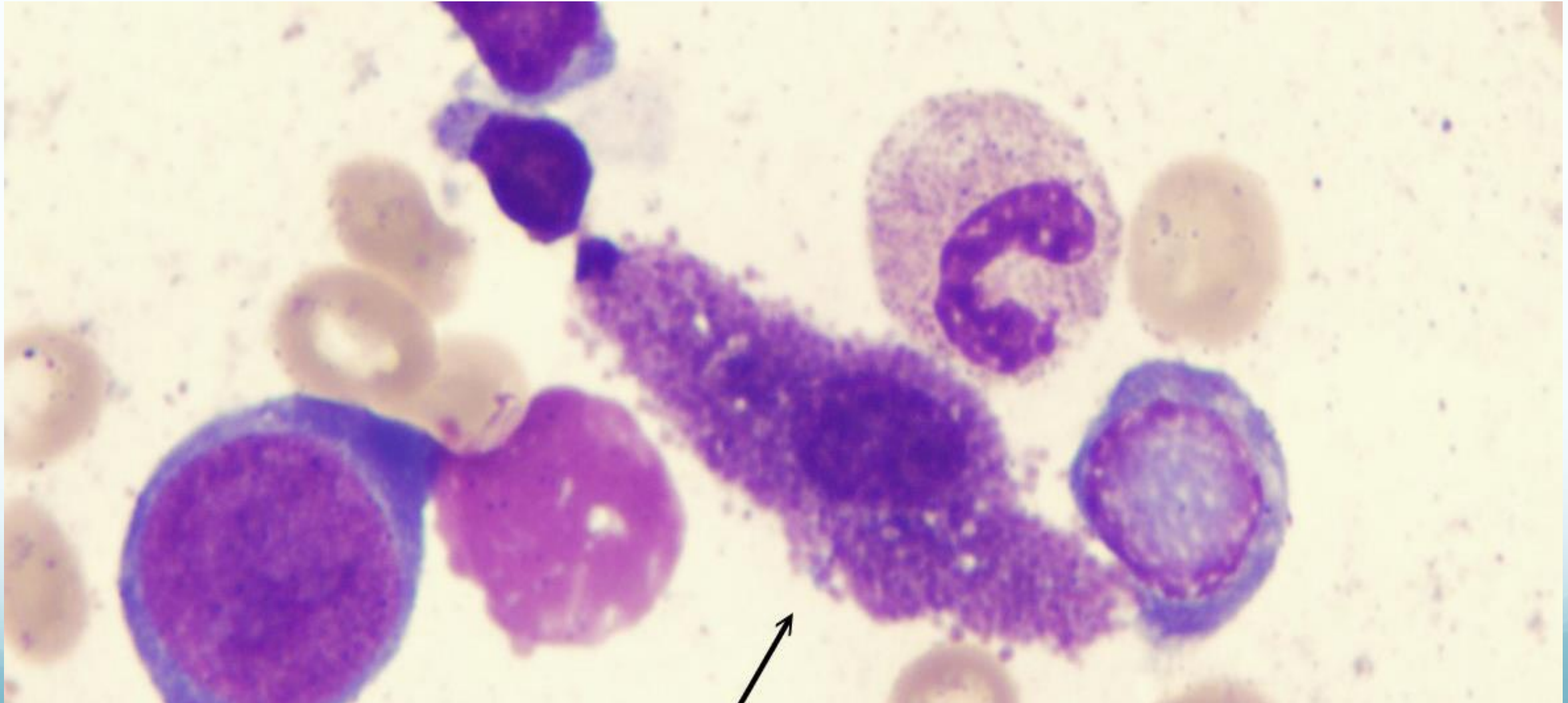
Bone Marrow Core Sample with CD117 Immunostaining

What is the *KIT* Mutation?

- *KIT* is a growth receptor on surface of mast cells.
- Mutation in *KIT* can cause mast cells to grow abnormally and in greater numbers.
- The most common mutation that affects patients with systemic mastocytosis is D816V, which we know as the *KIT* mutation.

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

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 specialist (usually a hematologist).

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

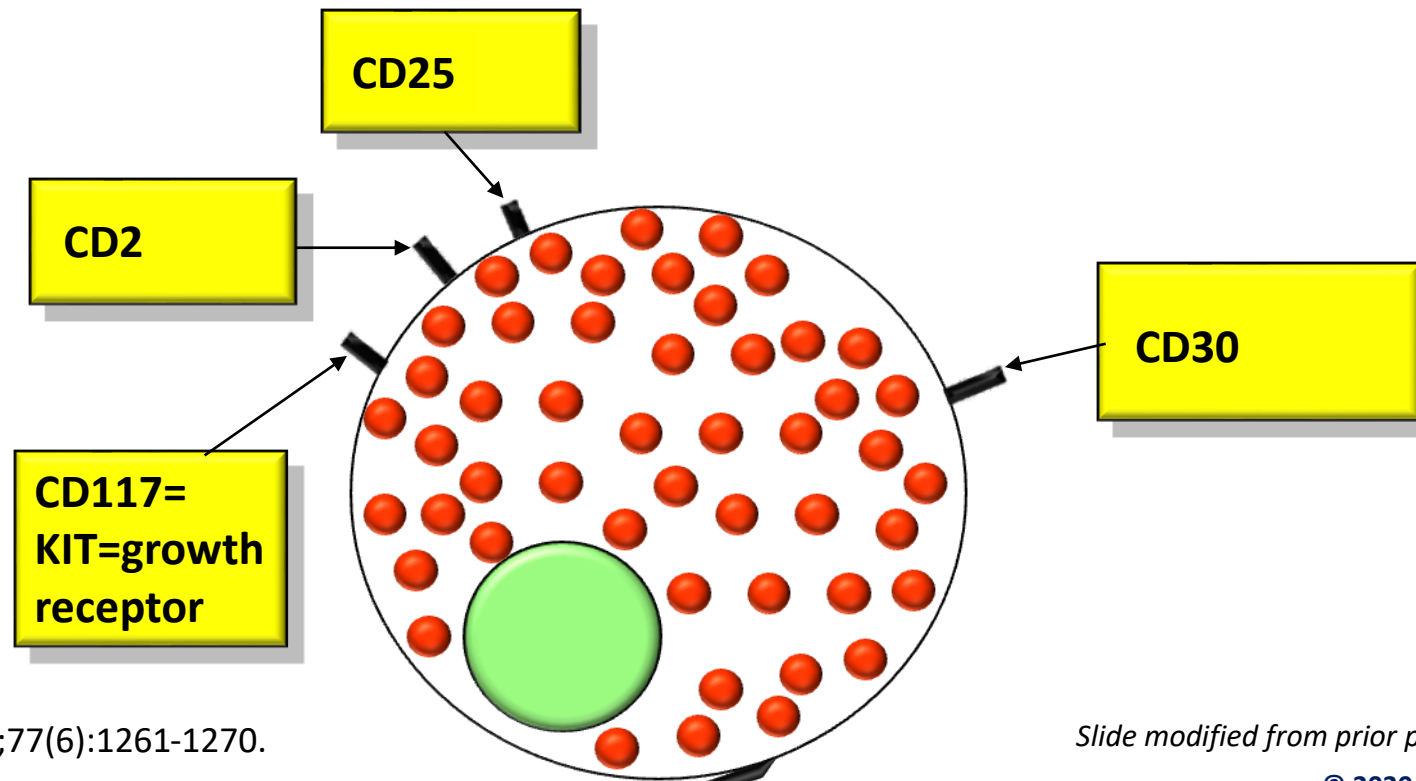
Clonal vs Non-Clonal Mast Cell Diseases

- *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 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.

Valent P, et al. Int Arch Allergy Immunol. 2012;157(3):215-25.

Abnormal Surface Markers in Systemic Mastocytosis

- Mutated CD117 (KIT D816V): KIT is also called CD117 - binds stem cell factor (SCF)
- CD2, CD25 & CD30: Lymphocyte surface markers not normally on mast cells



Cutaneous Mastocytosis (adult and pediatric) (CM)

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

Indolent Systemic Mastocytosis (adult and pediatric) (ISM)

- Well Differentiated Systemic Mastocytosis (WDSM)
- 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)
- Mast Cell Activation Syndrome, Secondary (MCAS)
- Mast Cell Activation Syndrome, Idiopathic (MCAS)

Hereditary alpha Tryptasemia (HaT) (potential mast cell disease/currently not yet classified)

Cutaneous Mastocytosis

Cutaneous Mastocytosis (adult and pediatric) (CM)

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

Hartmann K, et al. J Allergy Clin Immunol. 2016 Jan;137(1):35-45.

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.

Maculopapular Cutaneous Mastocytosis (MPCM)

- Most common 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 (monomorphic lesions may persist into adulthood versus polymorphic lesions).
- 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.

Hartmann K, et al. J Allergy Clin Immunol. 2016 Jan;137(1):35-45.

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.

Hartmann K, et al. J Allergy Clin Immunol. 2016 Jan;137(1):35-45.

Systemic Mastocytosis and Variants

- **Indolent Systemic Mastocytosis (adult and pediatric) (ISM)**
 - Well Differentiated Systemic Mastocytosis (WDSM)
 - 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)**

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

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)

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

Well Differentiated Systemic Mastocytosis (WDSM)

- Skin lesions, compact bone marrow mast cell (MC) clusters (>15 MCs), MCs with round-shape and larger, CD25-negative MCs, and elevated serum tryptase level (>20 ng/mL) (*may lack KIT D816V mutation*)
- Low MC burden which progresses, and a prolonged disease course
- May not meet 2008 World Health Organization (WHO) diagnostic criteria for SM, since the 3 minor criteria (spindle-morphology, aberrant CD2/CD25 expression, *KIT* D816 mutation) may be missing, and disease burden in bone marrow may be low.
- WDSM has been reported to show excellent responses to imatinib therapy in those who lack the *KIT* D816V mutation.

Valent P, et al. *Cancer Res.* 2017 Mar 15;77(6):1261-1270.

Álvarez-Twose I, et al. *J Allergy Clin Immunol.* 2016 Jan;137(1):168-178.e1.

Huang L, et al. *Medicine (Baltimore).* 2016 Oct;95(41):e4934.

Systemic Mastocytosis with Associated Hematologic Neoplasm (SM-AHN)

- 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.

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

Gotlib J, et al. Blood. 2013 Mar 28;121(13):2393-401.

Valent P, et al. Eur J Clin Invest. 2007 Jun;37(6):435-53.

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)

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

Gotlib J, et al. Blood. 2013 Mar 28;121(13):2393-401.

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**
- Extra fluid in the abdomen (ascites)
- Reduced nutrient uptake with weight loss and low blood albumin (a protein)

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

Gotlib J, et al. Blood. 2013 Mar 28;121(13):2393-401.

Smoldering Systemic Mastocytosis

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

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

Gotlib J, et al. Blood. 2013 Mar 28;121(13):2393-401.

Valent P, et al. Eur J Clin Invest. 2007 Jun;37(6):435-53.

Aggressive Systemic Mastocytosis

- Meets WHO mastocytosis criteria for diagnosis
- Mast cells on a bone marrow slide comprising <20% of the other 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)

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

Gotlib J, et al. Blood. 2013 Mar 28;121(13):2393-401.

Valent P, et al. Eur J Clin Invest. 2007 Jun;37(6):435-53.

Mast Cell Leukemia and Sarcoma

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
- Rare
- Aggressive course is typically seen

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

Gotlib J, et al. Blood. 2013 Mar 28;121(13):2393-401.

Valent P, et al. Eur J Clin Invest. 2007 Jun;37(6):435-53.

Extracutaneous Mastocytoma

- Extracutaneous mastocytomas are rare; prognosis is unknown.
- Tryptase- and chymase-positive mast cells with spindle shape or spherical forms are characteristic in the area around blood vessels.
- The differential diagnosis includes malignant melanoma, histiocytoma, eosinophilic granuloma, Kaposi sarcoma, and basal cell carcinoma.
- Extracutaneous mastocytoma has been removed from the 2016 updated WHO classification for mastocytosis, but is still represented in the ICD-10-CM coding system.

Valent P, et al. Cancer Res. 2017 Mar 15;77(6):1261-1270.

Castells MC. J Allergy Clin Immunol. 2006 Jun;117(6):1513-5.

Mast Cell Activation Syndrome (MCAS)

Patient demonstrates:

- Recurrent symptoms of mast cell activation, in two or more organ systems at the same time, that 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 F_{2α}, leukotriene E₄
- A response to mast cell mediator or mast cell stabilizer therapy

Valent et al. Int Arch Allergy Immunol. 2012;157(3):215-25.

Mast Cell Activation Syndromes

Mast Cell Activation Syndromes (adult and pediatric)

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

Valent et al. Int Arch Allergy Immunol. 2012;157(3):215-25.

Monoclonal Mast Cell Activation Syndrome (MMAS)

- 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.

Valent et al. Int Arch Allergy Immunol. 2012;157(3):215-25.

MCAS, Secondary

- Mast cell activation occurs as an indirect result of another disease or condition.
- IgE allergy may be the cause of secondary MCAS.
- Treatment involves therapy for the underlying cause as well as antimediator and mast cell stabilizing therapy.

Valent et al. Int Arch Allergy Immunol. 2012;157(3):215-25.

MCAS, Idiopathic

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

Valent et al. Int Arch Allergy Immunol. 2012;157(3):215-25.

Hereditary Alpha Tryptasemia

- Hereditary alpha tryptasemia (HaT) is an autosomal dominant genetic disorder caused by a duplication or triplication of the alpha-tryptase gene (sometimes, even more copies of the gene are found).
- If you have elevated tryptase with or without SM, it is important to be tested for HaT.

Lyons JJ, et al. Nat Genet. 2016;48(12):1564-1569.

Lyons JJ, et al. J Allergy Clin Immunol. 2014;133(5):1471-1474.

HaT (continued)

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

Lyons JJ, et al. Nat Genet. 2016;48(12):1564-1569.

Lyons JJ, et al. J Allergy Clin Immunol. 2014;133(5):1471-1474.

Is hereditary alpha tryptasemia a form of mast cell activation syndrome (MCAS)?

It is unclear whether mast cell activation plays a role in hereditary alpha tryptasemia (HaT).

More research needs to be done to determine:

1. How does HaT affect patients who also have MCAS?
2. Can the increased tryptase cause symptoms without mast cell activation?
3. Can the increased tryptase intensify normal mast cell activation?

Lyons JJ, et al. Nat Genet. 2016;48(12):1564-1569.

Lyons JJ, et al. J Allergy Clin Immunol. 2014;133(5):1471-1474.

How can I get tested and treated for HaT?

- A serum tryptase level (blood test) can help determine if your basal serum tryptase is over 10 ng/ml. If your serum tryptase is under 8 mg/ml, it is unlikely that you have HaT.
- Treatment is symptomatic. The course of HaT is not known at this time. More research is needed into this area.
- Gene by Gene makes a test specific for HaT.

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

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