

# **From MCAS to Mastocytosis**

Catherine Weiler, MD, PhD  
Co-Chair, Mayo Clinic Program for the  
study of Mast Cell and Eosinophil  
Disorders

Disclosures

**I HAVE NOTHING TO DISCLOSE**

## Objectives

- The symptom complex of mast cell disorders
- Review the different types and diagnostic criteria of mastocytosis
- Compare MCAS with mastocytosis

Talk is Divided in Two Sections

- 1. MASTOCYTOSIS**
- 2. MCAS**

## Patient 1.

- 55-year-old white male
- He reported a 10-year history of skin rash which has been gradually progressive. The rash is localized largely on the trunk both anteriorly and posteriorly with recent spread into the proximal thighs. He has had mild pruritus associated with this but otherwise very minimal symptoms
- He is aspirin allergic and has flushing with alcohol.

## Patient 1.

- Serum tryptase level mildly elevated at 17.6
- Skin biopsy elsewhere- macular cutaneous mastocytosis
- Bone marrow Biopsy: Systemic mastocytosis involving 5-10% of the bone marrow population
  - Quantitatively increased >15 mast cell aggregates containing spindle-shaped cells
  - Tryptase/ CD117 positive mast cells was also positive for surface expression of CD2 and CD25
  - KIT Asp816Val mutation was absent

## **Nomenclature and Abbreviations**

- CD117 is Kit, which is the growth receptor of mast cells
- SCF is the mast cell growth factor. It binds to CD117 (Kit)
- CD2 and CD25 are only expressed on lymphocytes. The abnormal expression of CD25 on mast cells is one of the diagnostic criteria of mastocytosis

## **Name Changes and Diagnostic Changes**

- Maculopapular cutaneous mastocytosis is the old urticaria pigmentosa and telangiectasia macularis eruptiva
- Smoldering mastocytosis is a new addition to the types of mast cell disorders

# Patient 1.

<input type="checkbox"/>	ALLERGY TE...				
<input type="checkbox"/>	ALLERGY T...				
<input type="checkbox"/>	Tryptase.....	<11.5 ng/mL	17.6 *		18May11
<input type="checkbox"/>	ENDOCRINE ...				
<input type="checkbox"/>	ENDOCRIN...				
<input type="checkbox"/>	TSH, Sens...	0.3-5.0 m...	2.2		18May11
<input type="checkbox"/>	ENDOCRIN...				
<input type="checkbox"/>	Calcitonin(...	pg/mL	929 *	@	18May11
<input type="checkbox"/>	Serotonin, ...	<=330 ng/mL	206		18May11
<input type="checkbox"/>	URINE CHEMI...				
<input type="checkbox"/>	URINE CHE...				
<input type="checkbox"/>	Creatinine ...	mg/dL	95 @		02May11
<input type="checkbox"/>	URINE HIST...				
<input type="checkbox"/>	N-Methylhi...	30-200 mc...	574 *	@	02May11
<input type="checkbox"/>	Collection ...	h	24 @		02May11
<input type="checkbox"/>	Urine Volu...	mL	2000 @		02May11

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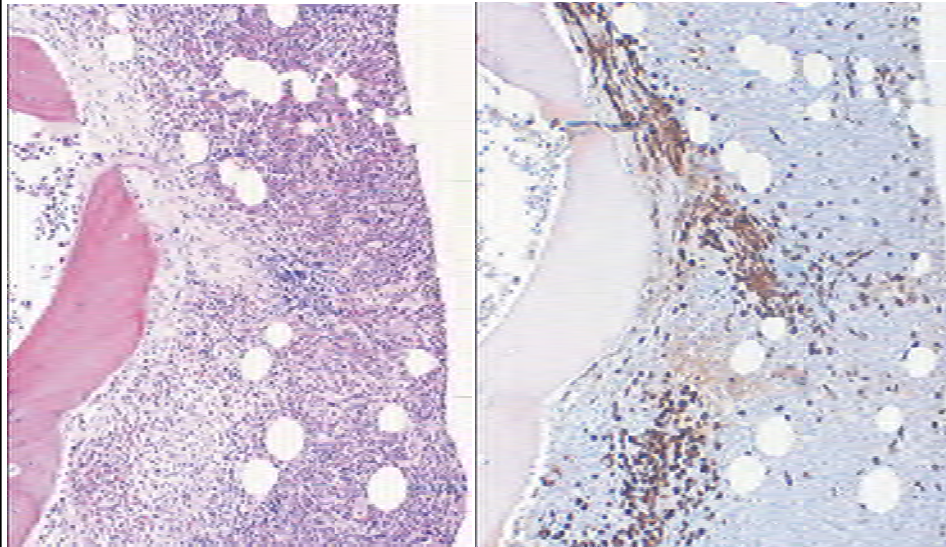
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## Patient 1.

- He was diagnosed with medullary thyroid carcinoma and underwent total thyroidectomy
- His calcitonin levels became normal

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## Patient 2.

- 53-year-old white female who presented in October of 2010
- She has a generalized skin rash that was biopsied in 2003.
- The diagnosis of mastocytosis
- She also had two to three different bone marrow biopsies, the last one was in 2008. She received "experimental chemotherapy" at MD Anderson in Texas
- She has generalized aches and pains; nausea and vomiting
- She does not have, flushing or diarrhea
- She has no dyspnea and no urticaria

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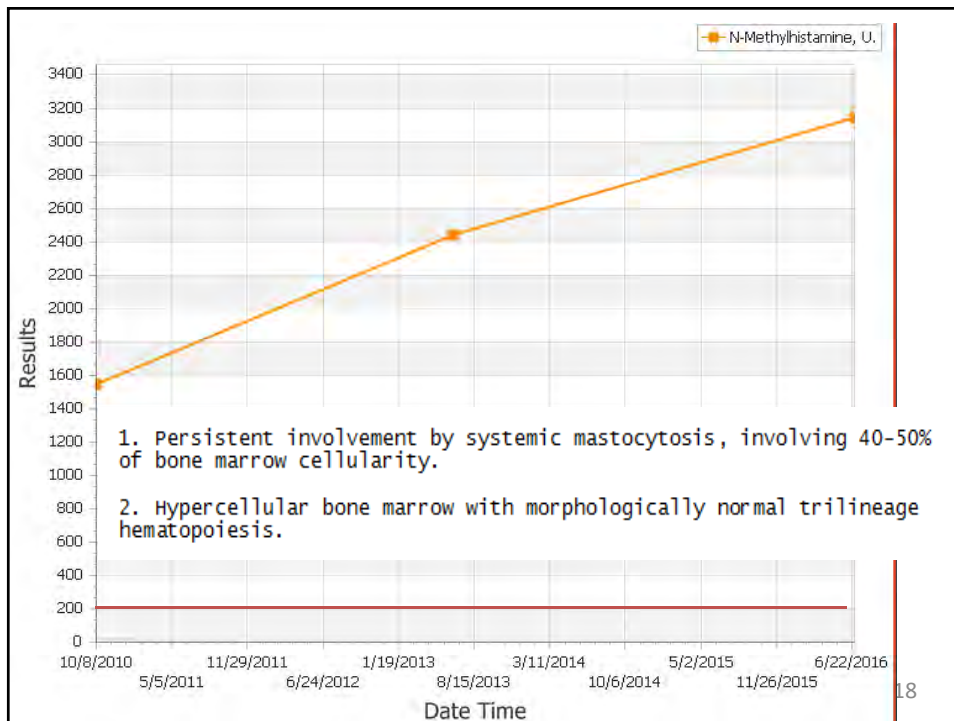
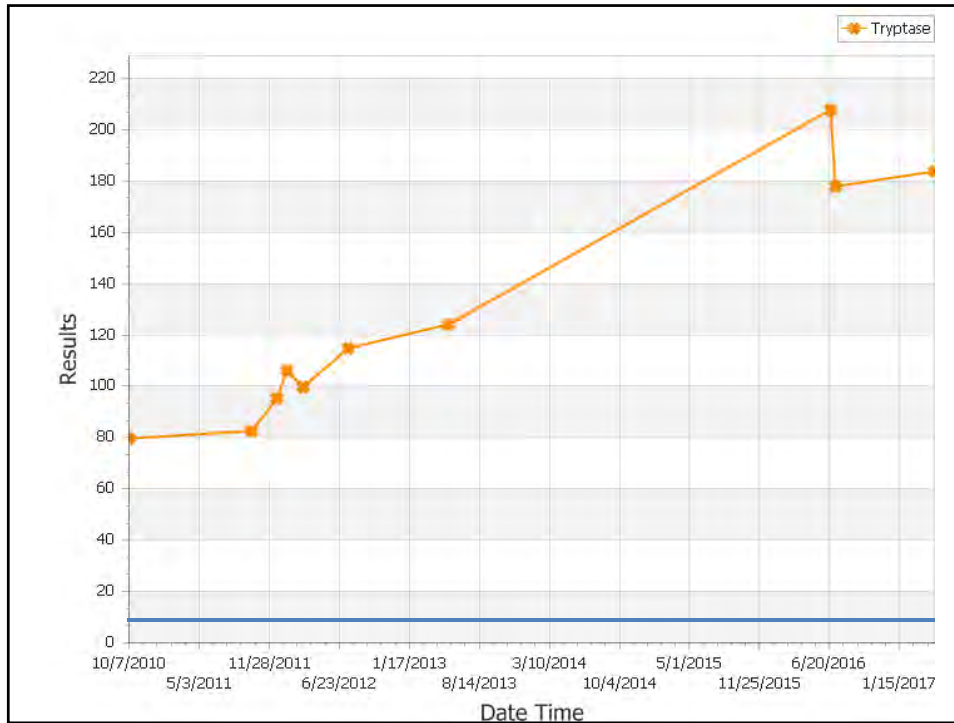
## Results 2010

- Bone marrow biopsy report:
  - **Atypical mast cell lesions replace 30% of the bone marrow space**
  - Immunohistochemical studies, bone marrow biopsy: mast cells are positive for **both tryptase and CD117**.
  - Flow cytometric immunophenotyping, bone marrow aspirate: Mast cell panel: **The CD117 (bright) and CD69 positive mast cells show aberrant coexpression of CD25**. The mast cells do not coexpress CD2.
  - Bone marrow, positive for KIT Asp816Val mutation

## Diagnoses

- **Bone marrow biopsy diagnosis 2010:**  
Systemic mastocytosis with mast cell lesions replacing approximately 30% of the bone marrow space
- **Bone marrow biopsy diagnosis 2016:**  
Systemic mastocytosis with mast cell lesions replacing approximately 40-50% of the bone marrow space
- **Skin biopsy:** Consistent with mastocytosis





## WHO Classification of Mastocytosis

- **Cutaneous mastocytosis (CM)**
  - Maculopapular CM (MPCM) = urticaria pigmentosa (UP)
  - Diffuse CM (DCM)
  - Mastocytoma of skin (cutaneous mastocytoma)
- **Systemic mastocytosis (SM)**
  - Indolent SM (ISM)
  - Smoldering SM (SSM)
  - SM with associated hematologic neoplasm (AHN)\*
  - Aggressive SM (ASM)
  - Mast cell leukemia (MCL)\*\*
- **Mast cell sarcoma (MCS)**

\*The previous term SM-AHNMD (SM with clonal hematologic non-mast cell-lineage disease) and the new term AHN can be used synonymously  
Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts  
Valent, Akin, and Metcalfe Blood. 2017;129(11):1420-1427; Cancer Res 2017; 77(6); 1–10

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## Diagnostic Criteria of Systemic Mastocytosis

### Major SM criterion:

Multifocal dense infiltrates of mast cells ( $\geq 15$  mast cells in aggregates) in bone marrow biopsies and/or in sections of *other extracutaneous organ(s)*

### Minor SM criteria:

1.  $>25\%$  of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in mast cell infiltrates detected on sections of visceral organs
2. *KIT point mutation* at codon 816 in the bone marrow or another extracutaneous organ
3. mast cells in bone marrow or blood or another extracutaneous organ exhibit *CD2 or/and CD25*
4. baseline serum *tryptase level*  $>20$  ng/ml (in case of an unrelated myeloid neoplasm, #4. is not valid as a SM criterion)

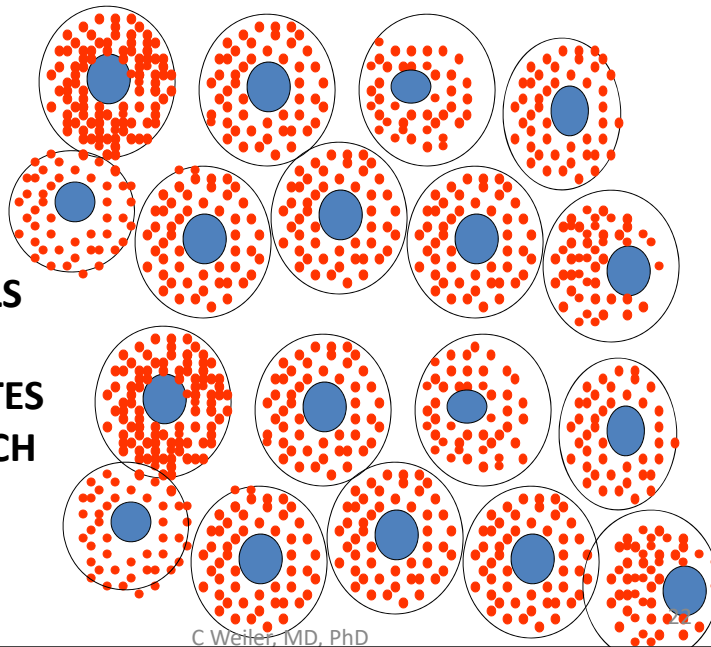
# Diagnostic Criteria for Systemic Mastocytosis

1 Major & 1 Minor  
Or 3 Minor Criteria

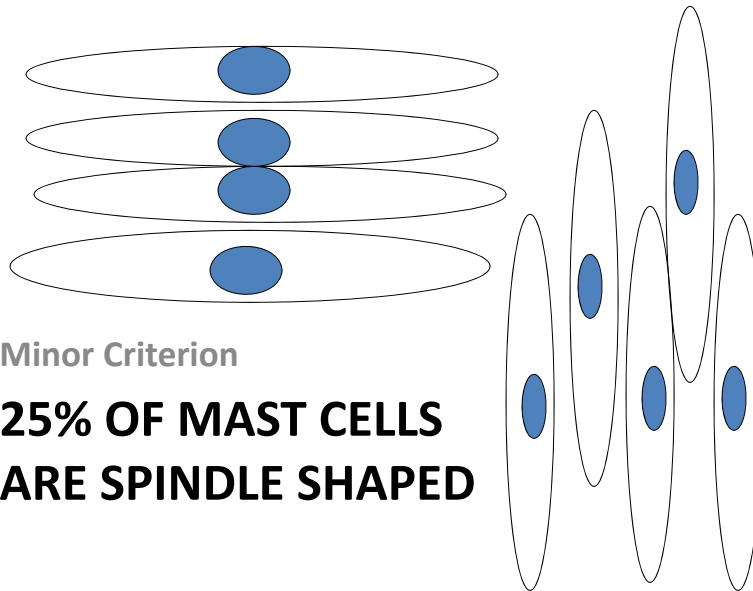
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Major  
Criterion  
**MAST CELLS  
IN  
AGGREGATES  
OF  $\geq 15$  EACH**



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Minor Criterion

**25% OF MAST CELLS  
ARE SPINDLE SHAPED**

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Minor Criterion

**SERUM TRYPTASE > 20 NG/ML**

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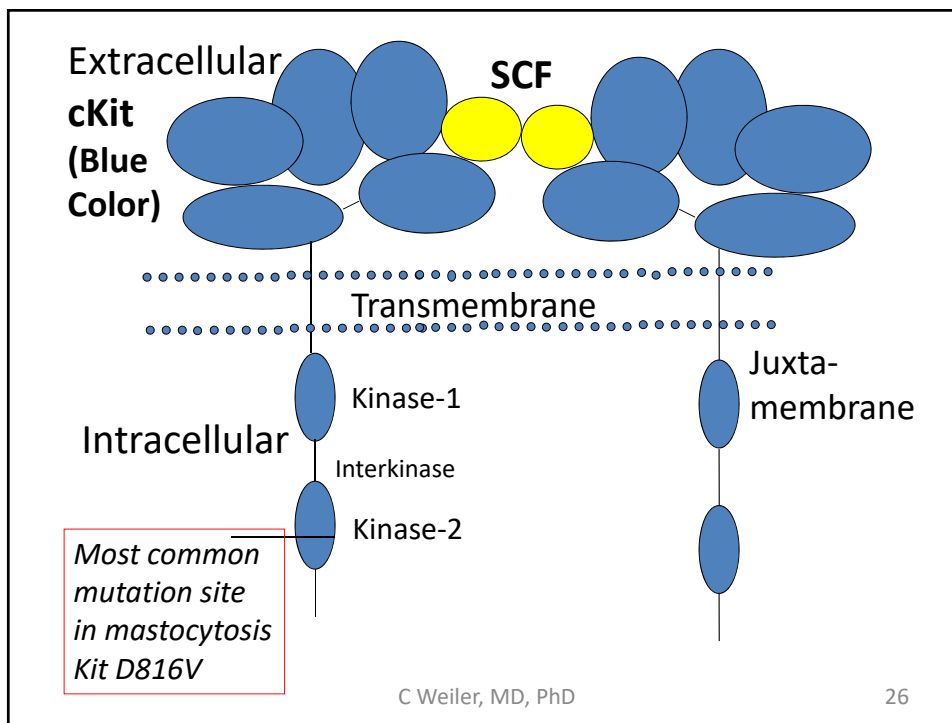
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Minor Criterion

## Positive Kit Asp816Val mutation (gain of function)

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Minor Criterion

**ABERRANT EXPRESSION OF CD25  
ON MAST CELLS**

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**MASTOCYTOSIS SYMPTOMS**

## **Mastocytosis**

- 30-40% of patients with mastocytosis have symptoms consistent with mast cell activation
- This rate is 1000-times that of the general population

## **Clinical Symptoms/Signs Associated with Systemic Mastocytosis**

- Urticaria pigmentosa; positive Darier's sign
- Mast cell mediator symptoms:
  - Flushing/warmth/pruritus/abdominal cramps/diarrhea/bronchospasm/tachycardia/hypotension
  - Symptoms respond to epinephrine administration & administration of medications targeting mast cell mediators

## **Clinical Symptoms/Signs Associated with Systemic Mastocytosis**

- Anaphylaxis to venom stings
- Eosinophilia
- Anaphylactic response to NSAIDs (90-95% of mastocytosis patients do tolerate them)

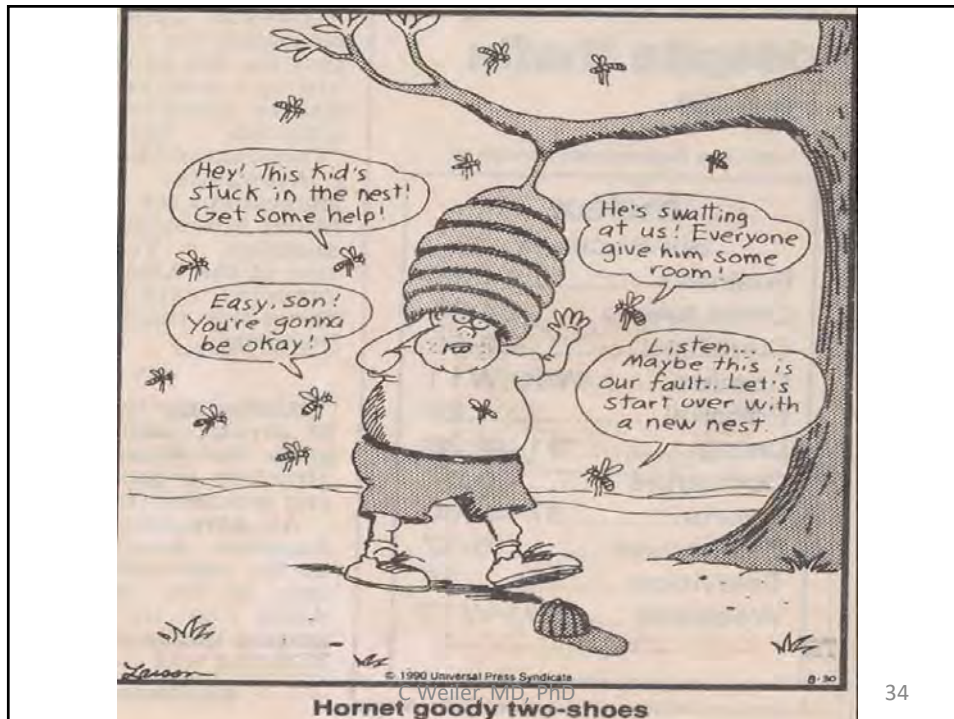
## **Mastocytosis Triggers**

- Exercise
- Heat
- Venomous insects such as hymenoptera, fire ants, mosquito bites, deer and horse flies
- Drugs- opioids- aspirin
- Alcohol
- Contrast dye





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Hornet goody two-shoes

## Hymenoptera Anaphylaxis in Patients with Mastocytosis

- Patients with MC disorder who experience hymenoptera sting present with severe hypotension in the **absence of urticaria or angioedema**
- [Curr Allergy Asthma Rep.](#) 2015 Aug;15(8):49

## What to Look for:

- **Cutaneous mastocytosis**
  - Most adults with UP have SM
  - Most children with cutaneous mastocytosis outgrow it
- **Mediator symptoms**
  - Other suggestive clinical features (bee sting anaphylaxis)

## What to Look for:

- **Response to MC mediator blockade**
- **Increased (baseline or symptom-associated)**
  - mast cell mediator levels: tryptase; N-methyl histamine;  $11\beta$ -PGF<sub>2a</sub>; LTE<sub>4</sub>
- **Confirmatory: bone marrow biopsy**

## Therapy of Anaphylaxis in Patients with Systemic Mastocytosis

- **Injectable epinephrine** should be used immediately—carry at least two injectable units
- For those with concomitant insect venom allergy, **venom immunotherapy for life** should be considered.

## **Kit Expression in Tissues**

- Mast cells
- Hematopoietic stem cells
- Germ cells
- Melanocytes
- Gastrointestinal Cajal Cells
- Epithelial cells
- Subset of neurons in the cerebellum

### **Part Two**

## **MAST CELL ACTIVATION SYNDROMES (MCAS)**

## Classification of Mast Cell Activation Syndromes

1. Primary (clonal) MCAS
2. Secondary MCAS
3. Idiopathic MCAS

## Primary (Clonal) MCAS: MC Have Kit-Mutation

- **Systemic Mastocytosis** according to WHO criteria
- **Monoclonal Mast cell activation syndrome (MMAS)**
  - Insufficient criteria met for SM, but evidence of clonal MC
  - Unknown behavior

## **Secondary and Idiopathic MCAS**

### **Secondary MCAS**

- Underlying inflammatory disease, often IgE-dependent allergy, but no mutated MC's

### **Idiopathic MCAS**

- Many fall under this heading

## **Clinical Symptoms/Signs Associated with idiopathic MCAS**

- Flushing/warmth/pruritus/abdominal cramps/diarrhea/bronchospasm/tachycardia/hypotension
- Symptoms respond to epinephrine administration & administration of medications targeting mast cell mediators

## Mast Cell Activation Syndromes (MCAS) Diagnostic Criteria

1. Patients manifest recurrent or chronic systemic *symptoms of mast cell activation*
2. Involvement of MC's can be documented by *contemporaneous increase of serum tryptase or other MC mediators* (urine).
3. Patients *respond to MC mediator-targeting medications* (mediator blockade, inhibition of mediator synthesis or MC stabilizing)

## Symptoms **NOT** Mast Cell Related

- Hypertensive spells
- Symptoms that improve with medications not targeting mast cell mediators
- Seizure activity; incontinence
- (Delayed) problems with memory
- Dementia
- Chronic recurrent headaches
- Chronic hives; atopic dermatitis or eczema
- Delayed reactions to medications
- Rhinitis or rhinosinusitis
- Food allergy
- Non-anaphylactic reactions to bee stings, fire ants, horseflies
- Arthritic complaints involving small joints or involving muscles

Diagnosis

## WHO GETS THE BONE MARROW BIOPSY?

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## REMA Score for Predicting Mast Cell Clonality and Systemic Mastocytosis

- The REMA score consisted of the assignment of positive or negative points as follows:
- male (+1), female (-1),
- sBt <15 g/l (-1) or 1 25 g/l (+2),
- Presence (-2) or absence (+1) of pruritus, hives or angioedema
- Presence (+3) of presyncope or syncope.

» **Validation of the REMA Score for Predicting Mast Cell Clonality and Systemic Mastocytosis in Patients with Systemic Mast Cell Activation Symptoms** Int Arch Allergy Immunol 2012;157:275–280  
DOI: 10.1159/000329856

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## Validation of the REMA Score for Predicting Mast Cell Clonality and Systemic Mastocytosis

- Molecular studies revealed the presence of clonal MC in 68/80 SM cases and in 11/78 patients who did not meet the criteria for SM
- ROC curve analyses confirmed the greater sensitivity and a similar specificity of the REMA score versus sBt levels (84 vs. 59% and 74 vs. 70% for MC clonality and 87 vs. 62% and 73 vs. 71% for SM, respectively)

» **Validation of the REMA Score for Predicting Mast Cell Clonality and Systemic Mastocytosis in Patients with Systemic Mast Cell Activation Symptoms** *Int Arch Allergy Immunol* 2012;157:275–280  
DOI: 10.1159/000329856

## Netherlands Recommendations

- In a patient with normal skin the risk of ISM is very low if tryptase is  $<10 \mu\text{g/l}$
- If tryptase is  $\geq 10 \mu\text{g/l}$  and MH, MIMA are normal the risk of ISM is low
- If MH and MIMA are elevated the risk of ISM is high
- M gender and insect venom anaphylaxis are additional risk indicators.
- No BM exam in patients without UP if tryptase is  $<10 \mu\text{g/l}$

– *Neth J Medicine* 2011; 69:309-17

## Multicenter Recommendations

- If KIT D816V is detected and/or tryptase is >25–30 ng/ml, with or without, clinical or laboratory features to suggest ISM or another hematologic neoplasm, a BM exam is recommended
- If KIT D816V is negative and symptoms of ISM or another hematopoietic disorder, are absent, then no need for BM exam.

Valent P, et al. **Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis.** *Allergy* 2014;69:1267–1274.

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## Therapy of **Clonal** Mast Cell Disorders

- **ANTIMEDIATOR THERAPY**
  - Epinephrine
  - Antihistamines
  - Ketotifen
  - Cromolyn
  - Anti-leukotrienes
  - Aspirin
  - Omalizumab
  - Glucocorticoids
  - Bisphosphonates
  - Ultraviolet-A irradiation
- **CYTOREDUCTIVE THERAPY**
  - IFN-  $\alpha$  and cladribine are the most commonly used cytoreductive agents with overall response rates around 50–70%
  - Imatinib is **not** indicated in the majority of patients as it is ineffective against D816 V KIT mutation
  - Midostaurin

Pharmacotherapy of mast cell disorders. [Curr Opin Allergy Clin Immunol.](#) 2017 May 31. doi: 10.1097/ACI.0000000000000377. [Epub ahead of print] [Gülen T<sup>1</sup>](#), [Akin C.](#) 52

## Therapy of **non-Clonal** Mast Cell Disorders

- ANTIMEDIATOR THERAPY

- Epinephrine
- Antihistamines
- Ketotifen
- Cromolyn
- Anti-leukotrienes
- Aspirin
- Glucocorticoids
- Bisphosphonates
- Ultraviolet-A irradiation

Pharmacotherapy of mast cell disorders. [Curr Opin Allergy Clin Immunol](#). 2017 May 31. doi: 10.1097/ACI.0000000000000377. [Epub ahead of print] [Gülen T<sup>1</sup>](#), [Akin C](#). 53

## Don't Do This.



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**Thank you.**



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## **What are other Commonly Mistaken Diagnoses?**

- Carcinoid
  - Brief flush, worsened by epi vs SM
- Common flushing/climacteric flushing
- Disorders of hyper/hypo-hidrosis
- Panic attacks
- Simple faint; vasovagal episodes

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## Spells

- **Endocrine** (Ex: pheochromocytoma, thyrotoxicosis, medullary thyroid carcinoma, insulinoma, hypoglycemia)
- **Cardiovascular** (labile HTN, deconditioning, pulmonary edema, syncope???, orthostatic hypotension, paroxysmal arrhythmias)
- **Neurologic** (postural orthostatic tachycardia syndrome, autonomic neuropathy, migraine headache, seizure disorders, stroke, cerebrovascular insufficiency)
- **Pharmacologic** (withdrawal of adrenergic inhibitor, MAO treatment + tyramine sympathomimetic ingestion, illegal drug ingestion, chlorpropamide-alcohol flush, vancomycin-red-man syndrome)
- **Psychologic** (somatization disorder, hyperventilation)

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## Common Laboratory Errors in Diagnosing Systemic Mastocytosis

- **Urinary Histamine Measurements**
  - Instead of MIAA/n-Methyl Histamine (better)
- **Serum Histamine Measurements**-difficult inaccurate-
- **5-HIAA-** is for carcinoid
- **Intestinal Biopsies**-pitfalls
- **Bone Scans**-nonspecific

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