Mast Cell Activation Disorders

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Disclosures

- **Consultancies**
  - Novartis (Midostaurin trial)
  - Deciphera
  - Blueprint
  - Patara Pharma
  - Allakos

- **Patent**
  - LAD2 cell line (NIH)

- **Royalties**
  - Uptodate
Mast cells in health and disease

- Mast cells are important components of our innate immune system
  - No human described without mast cells
  - Present in early vertebrates
  - Neutralization of toxins
  - Elimination of external and internal invaders and response to stress signals
- Mast cell activation is normal and necessary for the maintenance of a healthy state
- When does it become pathologic (disorder)
  - 1. Problem in mast cell itself (production, apoptosis, activation): Primary
  - 2. Excessive response to triggers: Secondary
Mast Cell Disorders

Activation

- Primary (clonal)
- Secondary (non-clonal)
- Idiopathic

Proliferation

- Mastocytosis
- Myelomastocytic conditions
- Mast cell hyperplasia
Mast Cells in Allergic Reactions

- B cell
- Th₂ cell
- Antigen
- IgE
- Mast cell
- IL4
- IgE Receptors
Mast cell degranulation by Substance P

Clinically Relevant Mediators Released from Mast Cells and Putative Effects.

- **Cardiovascular**
  - Hypotension
  - Syncope or near syncope
  - Light-headedness
  - Tachycardia

- **Cutaneous**
  - Flushing
  - Pruritus
  - Urticaria
  - Angioedema

- **Digestive**
  - Abdominal cramps
  - Diarrhea
  - Esophageal reflux
  - Nausea and vomiting

- **Mast-Cell Activators**
  - Allergens, bacteria, cytokines, drugs, fungi, peptides, toxins, and viruses

- **Mast cells**
  - CRH, chymase, histamine, interleukin-6, PAF, renin, TNF, tryptase

- **Musculoskeletal**
  - Aches
  - Bone pain
  - Osteopenia
  - Osteoporosis

- **Neurologic**
  - Anxiety
  - Depression
  - Decreased concentration and memory
  - Insomnia
  - Migraines

- **Respiratory**
  - Nasal congestion
  - Nasal pruritus
  - Shortness of breath
  - Throat swelling
  - Wheezing

- **Systemic**
  - Fatigue
  - Generalized malaise
  - Weight loss

- **Neurologic**
  - Anxiety
  - Depression
  - Decreased concentration and memory
  - Insomnia
  - Migraines

The Mastocytosis Society survey of 426 patients

- Cutaneous: 23%
- Systemic: 45%
- MCAD: 21%
- IA: 1.6%
- Not sure: 1.6%
- Other: Not answered

Jennings et al., The Mastocytosis Society Survey, 2014, JACI-In Practice
Mast Cell Activation Syndrome: Proposed criteria

Akin, Valent and Metcalfe, 2010. JACI

1. Recurrent episodic symptoms consistent with MC activation in at least 2 organ systems
   Skin, GI, cardiovascular, respiratory, nasoocular

2. Positive response to treatment with medications targeting mast cell mediators
   H1 and H2 antihistamines, cromolyn

3. Biochemical evidence of mast cell activation
   Tryptase, urine N-MH or PGD2

4. Rule out primary and secondary causes and other defined idiopathic entities
Differential diagnosis of anaphylaxis

- More common disorders
  - Neurally mediated syncope
  - Acute angioedema
  - Acute asthma attack
  - VCD
  - Globus sensation
  - Anxiety, panic attacks, somatiform
  - Respiratory distress
  - MI, arrhythmias or stroke
  - Shock
  - Perioperative hypotension
Differential diagnosis of flushing

- Medications
  - Vancomycin, niacin, nitrates
- Alcohol
- Menopause
- Hormone secreting tumors:
  - Carcinoid
  - Pheochromocytoma
  - Medullary thyroid cancer
  - Benign cutaneous flushing
- Autonomic dysfunction
- Emotions
- Rosacea
- Food associated causes
  - Scromboidosis
Mast cell activation disorders: A mechanistic classification

- Primary (clonal)
  - Systemic mastocytosis
  - MMAS
- Secondary (non-clonal)
  - Allergic disorders
  - Chronic inflammatory and neoplastic disorders
  - Physical urticarias
- Idiopathic
  - Anaphylaxis
  - Angioedema
  - Urticaria
  - MCAS
WHO Diagnostic Criteria for Systemic Mastocytosis

Major +1 minor or 3 minor are needed

• Major:
  – Characteristic multifocal dense infiltrates of mast cells in bone marrow biopsy

• Minor:
  – Morphology of mast cells: Spindle shaped
  – Detection of a codon 816 c-kit mutation
  – Expression of CD25 by the bone marrow mast cell population
  – Serum tryptase >20 ng/ml
Defects found in nearly 30% of the children

Defects found in nearly 90% of adult SM cases, from ISM to MCL, and in 35% of the children

Monoclonal Mast Cell Activation Syndrome

- Does not meet the full WHO criteria for diagnosis of systemic mastocytosis
  - 1 or 2 minor criteria
- Tryptase <20 ng/ml
- No skin lesions
- Primarily a disorder of mast cell activation rather than proliferation
- Most cases remain with low mast cell burden
Bone Marrow Lesions in Mastocytosis and MMAS
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENDER</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>+1</td>
</tr>
<tr>
<td>Female</td>
<td>-1</td>
</tr>
<tr>
<td><strong>CLINICAL SYMPTOMS</strong></td>
<td></td>
</tr>
<tr>
<td>Absence of urticaria and angioedema</td>
<td>+1</td>
</tr>
<tr>
<td>Urticaria and/or angioedema</td>
<td>-2</td>
</tr>
<tr>
<td>Presyncope and/or syncope</td>
<td>+3</td>
</tr>
<tr>
<td><strong>TRYPTASE</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;15 ng/mL</td>
<td>-1</td>
</tr>
<tr>
<td>&gt;25 ng/mL</td>
<td>+2</td>
</tr>
</tbody>
</table>

*Baseline serum tryptase

**SCORE < 2: low probability of clonal MCAD**
**SCORE ≥ 2: high probability of clonal MCAD**

Sensitivity: 0.92  
Positive Predictive Value: 0.89

Specificity: 0.81  
Negative Predictive Value: 0.87

Alvarez Twose et al. JACI 2010:125:1269
Hymenoptera anaphylaxis and mast cell disease  
(Bonadonna et al. JACI, 123:680-686, 2009)

- 379 patients
- 44 (11.6%) had tryptase >11.4 ng/ml
  - 31 had anaphylaxis
  - 34 had a bone marrow biopsy
    - 21 (62%) had systemic mastocytosis
    - 9 had MMAS
    - All with anaphylaxis had clonal mast cell disease

**Conclusions:**
- Serum tryptase should be checked in all patients with anaphylactic hymenoptera reactions
- A bone marrow examination is indicated for patients with elevated baseline tryptase
Case 1: MCAS?

- 45 year old woman with episodic hives, associated with flushing, abdominal pain and lightheadedness
- Fainting in some but not all episodes
- Episodes last about 30 minutes and resolve
- Feels completely fine between the episodes
- Baseline tryptase 4.5 ng/ml, increased to 30 ng/ml in one episode
Case 2: MCAS?

- 58 year old woman
- PMH: Allergic rhinitis, PTSD, depression
- Sx: Mental fogginess, fatigue, muscle pain, flushing
- Triggers: Environmental exposures, perfumes, stress
- H/o allergic rhinitis
- Tryptase: 4.4 ng/ml, urinary N-MH normal, PGD2: 440 mg/gr creatinine (normal <350)
- Memory problems had a response to cromolyn
- Diagnosed as MCAS by an outside allergist
MCAS: Mediators

- **Tryptase**
  - Normal median 4.5-5 ng/ml. >11.4 ng/ml reported as elevated
  - Significant elevation in mast cell activation is 20% baseline + 2 ng/ml

- **Urinary histamine metabolites**
  - M-methylhistamine
  - MIMA

- **Urinary PGD2 or 11-b-PGF2**

- **Urinary LTE4**
Tryptase release after anaphylaxis

Schwartz, LB. Immunology Allergy Clinics of N Amer. August 2006
Elevated baseline tryptase levels
(normal <11.4 ng/ml, median 5 ng/ml)

- Mastocytosis:
  - Diagnosis
  - Monitoring cytoreductive therapy
- Chronic kidney disease
- Myeloid neoplasms
  - AML
  - Chronic eosinophilic leukemia
  - Myelodysplastic syndromes
- Mast cell hyperplasia
  - Bone marrow suppression, severe anemia, drugs
- Familial alpha hypertryptasemia
- Idiopathic
Familial tryptase elevations in patients with atopy and connective tissue abnormalities


- 9 families with elevated tryptase levels
- Occurs in up to 6% of population
- Genetic lesion recently identified:
  • Extra copy of alpha tryptase gene inherited in an autosomal dominant fashion
  • Clinical significance unknown:
    - No evidence of mast cell activation
Table 1 Clinical features and gene-dose effects in hereditary α-tryptasemia syndrome

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Hereditary α-tryptasemia syndrome (α)</th>
<th>TPSAB1 duplication (ααα)</th>
<th>TPSAB1 triplication (αααα)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum trypase, ng/ml Median Inte...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median Range</td>
<td>15.9 12.6–20.7</td>
<td>14.3 11.6–17.8</td>
<td>23.4 19.8–26.4</td>
</tr>
<tr>
<td>Systemic venom reaction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n</td>
<td>15/96</td>
<td>11/73</td>
<td>4/15</td>
</tr>
<tr>
<td>Flushing/pruritus</td>
<td>%</td>
<td>16</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>IBS (Rome III)</td>
<td>n</td>
<td>34/70</td>
<td>26/53</td>
<td>7/12</td>
</tr>
<tr>
<td>Chronic gas troesophageal reflux symptoms</td>
<td>n</td>
<td>62/96</td>
<td>42/73</td>
<td>15/15</td>
</tr>
<tr>
<td>Congenital skeletal abnormality&lt;sup&gt;c&lt;/sup&gt;</td>
<td>n</td>
<td>25/96</td>
<td>14/73</td>
<td>8/15</td>
</tr>
<tr>
<td>Retained primary dentition</td>
<td>n</td>
<td>20/96</td>
<td>12/73</td>
<td>7/15</td>
</tr>
<tr>
<td>Hypermobility (Beighton score ≥4)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>n</td>
<td>14/50</td>
<td>11/30</td>
<td>3/13</td>
</tr>
<tr>
<td>COMPASS 31&lt;sup&gt;e&lt;/sup&gt;</td>
<td>n</td>
<td>33/70</td>
<td>26/57</td>
<td>5/11</td>
</tr>
<tr>
<td>Positive tilt-table test 11≤≥8</td>
<td>n</td>
<td>6</td>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>n</td>
<td>43/96</td>
<td>31/73</td>
<td>11/15</td>
</tr>
<tr>
<td>Body pain/headache</td>
<td>n</td>
<td>45/96</td>
<td>32/73</td>
<td>11/15</td>
</tr>
<tr>
<td>Sleep disruption</td>
<td>n</td>
<td>37/96</td>
<td>23/73</td>
<td>11/15</td>
</tr>
</tbody>
</table>

IBS, irritable bowel syndrome; ND, not able to determine. Statistically significant differences are marked in bold. NS, not significant.

<sup>a</sup>Comparison of duplication (ααα) and triplication (αααα) carriers at TPSAB1. <sup>b</sup>Systemic immediate hypersensitivity reaction consistent with IgE-mediated response to stinging insects, as described in the Supplementary Note. <sup>c</sup>Presence of a congenital skeletal malformation (the complete list of malformations identified is provided in the Supplementary Note) or diagnosis of EDS. <sup>d</sup>Only individuals over 12 years of age and who could be directly visualized were assessed and reported. <sup>e</sup>Number of individuals with a composite score above the upper 95% confidence interval of the median established in a healthy control cohort without increased copy number at TPSAB1.

Table 2 Self-reported clinical features among ClinSeq participants with and without identified TPSAB1 duplication on a single allele

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>TPSAB1 duplication (ααα)</th>
<th>WT TPSAB1</th>
<th>OR</th>
<th>RR</th>
<th>Value</th>
<th>Range</th>
<th>Value</th>
<th>Range</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic venom reaction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2/9</td>
<td>2/82</td>
<td>11.4</td>
<td>1.4–94.0</td>
<td>9.1</td>
<td>1.5–57.1</td>
<td>0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing/pruritus</td>
<td>5/9</td>
<td>13/82</td>
<td>6.6</td>
<td>1.6–28.1</td>
<td>3.5</td>
<td>1.6–7.6</td>
<td>0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS (Rome III)</td>
<td>3/9</td>
<td>6/82</td>
<td>6.3</td>
<td>1.3–31.9</td>
<td>4.6</td>
<td>1.4–15.2</td>
<td>0.042</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic gastroesophageal reflux symptoms</td>
<td>7/9</td>
<td>39/82</td>
<td>3.9</td>
<td>0.8–19.7</td>
<td>1.6</td>
<td>1.1–2.5</td>
<td>0.158</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital skeletal abnormality&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1/9</td>
<td>3/82</td>
<td>3.3</td>
<td>0.3–35.5</td>
<td>3.0</td>
<td>0.4–26.2</td>
<td>0.346</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retained primary dentition</td>
<td>3/9</td>
<td>4/82</td>
<td>9.8</td>
<td>1.8–54.0</td>
<td>6.8</td>
<td>1.8–25.8</td>
<td>0.020</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMPASS 31&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4/9</td>
<td>11/82</td>
<td>5.2</td>
<td>1.2–22.3</td>
<td>3.3</td>
<td>1.3–8.3</td>
<td>0.038</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4/9</td>
<td>25/82</td>
<td>1.8</td>
<td>0.5–7.4</td>
<td>1.5</td>
<td>0.6–3.2</td>
<td>0.459</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body pain/headache</td>
<td>3/9</td>
<td>12/82</td>
<td>2.9</td>
<td>0.6–13.3</td>
<td>2.3</td>
<td>0.8–6.6</td>
<td>0.165</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep disruption</td>
<td>2/9</td>
<td>21/82</td>
<td>0.8</td>
<td>0.2–4.3</td>
<td>0.9</td>
<td>0.2–3.1</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IBS, irritable bowel syndrome; OR, odds ratio; RR, relative risk. Statistically significant differences are marked in bold.

<sup>a</sup>Systemic immediate hypersensitivity reaction consistent with IgE-mediated response to stinging insects, as described in the Supplementary Note. <sup>b</sup>Spina bifida occulta, congenital absence of spinous process, pectus excavatum, and tibial torsion. <sup>c</sup>Number of individuals with a composite score above the upper 95% confidence interval of the median established in a healthy control cohort without increased copy number of TPSAB1.

Treatment of mast cell activation syndromes

Clonal

\[ \downarrow \]

Non-clonal

\[ \downarrow \]

H1 + H2 antihistamines, anti-leukotrienes, cromolyn

\[ \downarrow \]

Ketotifen

\[ \downarrow \]

Omalizumab, glucocorticoids

\[ \downarrow \]

Cytoreduction: IFN-alpha, cladribine
FIG 1. Chronologic course of anaphylaxis before and after therapy. Upper panel, patient 1; lower panel, patient 2. Anaphylactic events are represented by closed arrows. Omalizumab therapy initiated at time 0. The serum tryptase on the y-axis is represented as solid circles above each graph.
Midostaurin inhibits IgE mediated mast cell and basophil activation
Krauth et al. Allergy 2009
Decreased Frequency of MSAS Symptoms with midostaurin

Baseline MSAS (n = 37)
Best TMSAS value on treatment (n = 37)
MCAS
Future directions

• Prospective clinical studies (natural history, prognosis, validate criteria, therapeutic)
• New markers of mast cell activation
• Molecular mechanisms
  – Known gene defects (D816V c-kit)
  – New targets
MCAS: when a referral is appropriate

- Patients diagnosed with mastocytosis
- Episodic symptoms of flushing, presyncope or syncope, associated with GI symptomatology
- Recurrent anaphylaxis with objective findings
- Elevated tryptase levels
- Bee venom anaphylaxis
When a referral to allergy is not high yield

- Patients with multiple food and environmental intolerances,
- Weight loss due to food avoidance,
- Subjective symptoms,
- Patients with primarily neurocognitive symptoms
MCAS: Open questions

• Is there a chronic form of mast cell activation?
• Cutoff levels and specificity of urinary mediators
• Are Postural Orthostatic Tachycardia Syndrome and Ehlers Danlos Syndrome (hypermobility type) associated with MCAS?
• Is familial tryptasemia really a disorder?
  – Is there a confirmed phenotype?
  – If so, is tryptase involved in its pathology?
  – Is it associated with mast cell activation?