Mast Cell Activating Disorders

AAAAAI

2013
DISCLOSURE

Consultant/Speaker
Mylan, Sanofi-Aventis, Merck, Meda, Genentech
Baxter, Teva
Objectives

• To recognize mast cell activating disorders (MCAD)

• To differentiate MCAD from idiopathic anaphylaxis

• To manage MCAD
Mast Cell Activating Syndrome: Many Names, Same Condition

- MAD: mast cell activating disorder
- c-MCAD: clonal mast cell disorders
- MCAD: mast cell activating disorders
- MACS: mast cell activation syndromes
- MCD: mast cell clonal disorder
- MCAS: mast cell clonal activating syndrome
A Little History
Hyperadrenergic Postural Tachycardia Syndrome (POTS), A Mast Cell Activation Disorder

- Postural tachycardia syndrome (POTS) is a disabling condition that commonly affects otherwise normal young females
- “Here we describe POTS patients with MCA (MCA+POTS), diagnosed by episodes of flushing and abnormal increases in urine methylhistamine”

*Hypertension* 2005; 45: 385-390, 2005
Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with "idiopathic" anaphylaxis

- 12 patients with IA
- None with classic Bx for SM
- 5 had evidence of 1 or more minor criteria for mastocytosis.
- 3 had activating mutation of c-kit(D816>V)

Elevated Tryptase with Anaphylaxis a not Systemic Mastocytosis

- Eight patients had elevated baseline serum tryptase levels ranging between 15.4-36.5 ng/ml.

- Flushing was the most frequently reported symptom, followed by gastrointestinal symptoms. Two patients had recurrent unexplained anaphylaxis.

- Hematologic parameters were unremarkable in all patients. D816V c-kit mutation associated with mastocytosis was not detectable in any patient.

None with Classic Biopsy for Systemic Mastocytosis
Dx Criteria for Systemic Mastocytosis

- **Major**: Multifocal dense aggregates M.C. in Bone Marrow
- **Minor**
  - Spindle shaped M.C.
  - 816 c-kit mutation
  - CD 117, 2, 25
  - Serum tryptase > 20 ng/ml

3 Minor or 1 Major and 1 Minor

Leukemia research 25:603, 2001
The “Old” Nosology

Human Anaphylaxis

Immunologic

- IgE, FcεRI
  - foods, venoms, latex, drugs

- Other
  - blood products, immune aggregates, drugs

Non-Immunologic

- Physical
  - exercise, cold

- Other
  - drugs

Idiopathic
The New Nosology
Mast cell activation disease (MCAD)

- Mast cell activation syndrome (MCAS)
- Mast leukemia
- Systemic mastocytosis (SM) defined by the WHO criteria
  - Indolent systemic mastocytosis
  - Smoldering systemic mastocytosis
  - Aggressive systemic mastocytosis
  - Systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease

Hematol Oncol. 2011; 4: 10
Position Paper

Int Arch Allergy Immunol 2012;157:215–225
DOI: 10.1159/000328760

Received: January 24, 2011
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Definitions, Criteria and Global Classification of Mast Cell Disorders with Special Reference to Mast Cell Activation Syndromes: A Consensus Proposal

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Typical clinical symptoms + transient increase in serum tryptase levels or transient increase of another established MC mediator + response to anti-mediator drugs

MCA

Monoclonal MCs (KIT D816V or other KIT exon 17 mutations)

Primary MCAS

3 minor or 1 major + 1 minor SM criteria

SM SY

CM SY

Secondary MCAS

1 or 2 minor and no major SM criteria

MIS criteria

No MIS

(Mono)clonal MCAS

Type I allergy of another underlying disease leading to MCA

No allergy, no other underlying disease, no monoclonal MCs and no MIS detected

Idiopathic MCAS
### Table 4. Classification of MCASs

<table>
<thead>
<tr>
<th>Category &amp; Variants</th>
<th>Proposed Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary MCAS</strong></td>
<td></td>
</tr>
<tr>
<td>Mastocytosis</td>
<td></td>
</tr>
<tr>
<td>(Mono)clonal MCAS</td>
<td>MCA criteria fulfilled and MC (mono)clonality proven (CD25+ MCs and/or KIT D816V)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary MCAS</strong></td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>MCA criteria fulfilled and criteria for the diagnosis of allergy or other diseases</td>
</tr>
<tr>
<td>Other underlying disorder</td>
<td>that can produce MCA fulfilled as well</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Idiopathic MCAS</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCA criteria fulfilled, but no disease that could lead to MCA diagnosed</td>
</tr>
</tbody>
</table>

**IDIOPATHIC ANAPHYLAXIS**
Dx Criteria for Systemic Mastocytosis

• Major: Multifocal dense aggregates M.C. in Bone Marrow

• Minor
  Spindle shaped M.C.
  816 c-kit mutation
  CD 117, 2, 25
  Serum tryptase > 20 ng/ml

3 Minor or 1 Major and 1 Minor

Leukemia research 25:603, 2001
C-KIT is Critical
CODON 816

MASTOCYTOSIS
C-kit receptor

MAST CELL
There Are Other Mutations

- Seventeen patients diagnosed with systemic mast cell activation disorder by means of a diagnostic questionnaire.

- “Here, we describe for the first time multiple novel disease-related alterations in c-kit gene transcripts (in particular, insertion of glutamine at position 252) in patients with a clinically manifested systemic mast cell activation disorder.”

Scandinavian J Gastroenterology
2007, Vol. 42, No. 9, Pages 1045-1053
There Are Other Mutations

- Eight patients (3 males, 5 females, age 16-70 years) had elevated baseline serum tryptase levels ranging between 15.4-36.5 ng/ml.

- Flushing was the most frequently reported symptom, followed by gastrointestinal symptoms. Two of the 8 patients presented with recurrent unexplained anaphylaxis.

- Hematologic parameters were unremarkable in all patients. D816V c- kit mutation associated with mastocytosis was not detectable in any patient.

Criteria for Diagnosis of MCAS (old)

• Absence of primary or secondary causes of mast cell degranulation, including mastocytosis
• Symptoms characteristic of mast cell mediator release affecting two or more systems
• Validated marker of degranulation
• Improvement with anti-mediator therapy

Criteria for Diagnosis of MCAS (new)

- Typical Symptoms
- Substantial transient increase in mast cell mediators (ST increase 20% + 2ng/ml) within 4 hours of a reaction
- A response to agents attenuating the production of or activities of these mediators
- Not mastocytosis

Valent et al; Int Archives Allergy Immunol 2012 157:215 -225
Differences in the Clinical Presentation of Anaphylaxis in Patients with Indolent Systemic Mastocytosis (ISM) versus Idiopathic Anaphylaxis (IA)

- Tryptase levels were significantly elevated with ISM compared to IA
- IA had significantly higher IgE
- Urticaria was more frequent with IA, Notably, no patients with ISM had urticaria during anaphylactic episodes

Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms

The Journal of Allergy and Clinical Immunology
Volume 125(6), Pages 1269-1278.e2, June 2010
MCAD vs IA

• 83 pts with MC activation Sx
• Two major groups: Clonal (51) and non-Clonal (32)
• 48 of the 51 Clonal met WHO mastocytosis criteria. All 51 had CD25+ mast cells and either cKit mutation or HUMARA (clonal human androgen receptor)
Features predictive of Clonal

• Male Sex
• Presyncopal or syncopal episodes in the absence of urticaria or angioedema
• There was also a higher frequency of CV problems and insect related episodes and higher baseline tryptase levels in the clonal group
Clinical features CISM vs NC ISM

Journal of Allergy and Clinical Immunology
Volume 125, Issue 6, Pages 1269-1278.e2, June 2010
Clinical features CISM vs NC ISM

Journal of Allergy and Clinical Immunology
Volume 125, Issue 6, Pages 1269-1278.e2, June 2010
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CLINICAL SYMPTOMS</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>TRYPTASE</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<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

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity: 0.92</th>
<th>Positive Predictive Value: 0.89</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Specificity: 0.81</td>
<td>Negative Predictive Value: 0.87</td>
</tr>
</tbody>
</table>

Journal of Allergy and Clinical Immunology  
Volume 125, Issue 6, Pages 1269-1278.e2, June 2010
<table>
<thead>
<tr>
<th>Sign or symptom: MCAS</th>
<th>Total (%)</th>
<th>n = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>17 (94)</td>
<td></td>
</tr>
<tr>
<td>Dermatographism</td>
<td>16 (89)</td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>16 (89)</td>
<td></td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>15 (83)</td>
<td></td>
</tr>
<tr>
<td><strong>Poor concentration and memory</strong></td>
<td>12 (67)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (67)</td>
<td></td>
</tr>
<tr>
<td><strong>Naso-ocular</strong></td>
<td>7 (39)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>7 (39)</td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>3 (17)</td>
<td></td>
</tr>
</tbody>
</table>

J Allergy Clin Immunol 2011;128:147-52.)
“SOFT” SYMPTOMS

CLASSIC MANIFESTATIONS
## Table 3. Symptoms considered typical for MCA by the members

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Consensus Level</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>95%</td>
<td>Flushing more common.</td>
</tr>
<tr>
<td>Pruritus</td>
<td>90%</td>
<td>Hives less common.</td>
</tr>
<tr>
<td>Urticaria</td>
<td>85%</td>
<td>Angioedema perhaps less characteristic</td>
</tr>
<tr>
<td>Angioedema</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>90%</td>
<td>Nasal symptoms more common.</td>
</tr>
<tr>
<td>Nasal pruritus</td>
<td>90%</td>
<td>Wheezing about the same.</td>
</tr>
<tr>
<td>Wheezing</td>
<td>70%</td>
<td>Throat swelling more common?</td>
</tr>
<tr>
<td>Throat swelling</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>90%</td>
<td>Hypotension, Headache, Diarrhea</td>
</tr>
<tr>
<td>Hypotension</td>
<td>95%</td>
<td>All more common in MCAS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>
So What Does All This Mean To Us?
The Causes of Anaphylaxis:
Select Cases (1002)

- IDIOPATHIC: 61%
- FOOD: 22%
- MEDICATIONS: 11%
- EXERCISE: 5%
- OTHER: 1%

Webb et al: J Allergy Clin Immunol 113:s241, 2004
Medical history

- Specific medical history with regard to a mast cell mediator release syndrome
- Specific physical examination for mast cell-induced cutaneous signs
- Determination of potential mast cell mediators
- Gastroscopy, coloscopy with biopsy
- Sonography of the internal organs
- Echocardiogram, 24-hour ECG, stress test
- Bone density measurement by DXA technique

Bone marrow biopsy to
- exclude hematologic non-mast cell lineage diseases
- detect a possible accumulation of mast cells
- detect possible morphologic/immunohistochemical/genetic pathological alterations of mast cells

Testing of drugs on tolerance

Suspected mast cell activation disease

Diagnosis: mast cell activation disease

Classification of the variant:
- Systemic mastocytosis according to the WHO criteria
- Mast cell activation syndrome

Basal chronic therapy to reduce mast cell activity
Symptomatic therapy if necessary to antagonize mast cell mediator-induced symptoms
SYMPTOMS

FLUSH
GI symptoms

Carcinoid
VIPoma

Shock

Mastocytosis

Urticaria
Angioedema

IA or MMAS
MANIFESTATIONS

Vipoma, Carcinoid

- Chromogranin A
- 5HIAA
- SP
- Pancreastatin
- Neurokinin
- etc

Mastocytosis
- MCAS
- Idiopathic anaphylaxis

- Tryptase
- Histamine
- Alpha-gal
- Skin test
- Bone Marrow
When do you do a bone marrow

- Tryptase greater than?
- Male sex
- Flushing
- GI sx
- Lack of urticaria
- Preysncope/synocpe
- Headache
- CNS Sx
- **Tryptase normal**
Bone Marrow
Tryptase
CD117
CD25
CD2
Histology
Treatments

- Anti-mediator drugs
- Omalizumab
- Prednisone
- Cyclosporine/Tacrolimus
- Mycophenylate mofetil
- Methotrexate
- Azathioprine
- Imatinib
Conclusions

• IA is a subcategory of MCADs
• It can only be definitively distinguished from ISM or non ISM clonal MCAD by bone marrow Bx
• But there are several clinical features that point toward a clonal disorder
Thank You