Mast cell disorders - more than just hives

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Objectives

• 1. To discuss the role of mast cell in disease

• 2. To present the main mast cell disorders: classification and diagnosis (mastocytosis, mast cell activation syndrome, idiopathic anaphylaxis)

• 3. To discuss management and our call for a new registry.
Mast cells (MCs)

- Formed in bone marrow as CD13+/CD34+/CD117+ multipotent haematopoietic progenitors.
- Released to blood vessels in order to settle at the target tissue.
- Localized mainly in the surfaces of the mucosa.
- Often close to the blood and lymphatic vessels, below the epithelium, lining the respiratory, digestive, or genitourinary systems and in the skin

Physical stimuli – temp, pressure

RIG-I recognition of uncapped vRNA

TLR3

dsRNA

Comp (c5a)R

PAFRs

IL33

Degranulation (seconds):
- histamine,
- Tryptase,
- chymase

Lipid: Eicosanoids
- PGD2, PGF2
- LT, PAF

Cytokines, chemokines
- GF: TNFα, IL4, IL5, IL13, IL6, IL17, VEGF

Mas-related G protein-coupled receptor-x2 (MRGPRX2) for drugs (and similar for estrogen, prog, NT such as adenosine, cannabinoid, sub P or Ach)
2-year-old boy presented with a history of diffuse cutaneous hives since 3mo.

Was suspected to have milk allergy

Frequent symptoms flares associated with minimal trauma.

Trypatse =45 mcg/L

[ normal levels: 3.8-11.4 mcg/L]).

Skin biopsy :cutaneous mastocytosis and a test for C-KIT816 mutation was negative.

Tx:hydroxyzine 10mg daily, and ketotifen 1mg twice

Continued to experience frequent flares triggered by respiratory infections/minor trauma with blistering, and secondary scarring requiring monthly oral steroids treatment.
Mastocytosis: a debilitating disease

- Heterogeneous disease characterized by a clonal expansion of mast cells in various organs
- May be triggered by multiple provoking factors such as hot and cold baths, stress, and exercise
- Unpredictability of symptoms was found to be the greatest single cause of distress in patients living with mastocytosis
- Overall reduced quality of life
Mastocytosis = clonal mast cell activation (usually with c-KIT mutation)

Systemic (SM)
- When MC burden is low, tryptase may be normal but there still might be aggregates in BM.

Diffuse Cutaneous Mastocytosis

Urticaria pigmentosa = Urticaria pigmentosa is more accurately referred to as maculopapular cutaneous mastocytosis (MPCM)

mastocytoma

Indolent SM - skin lesions rare, Symptoms related to the release of mast cell mediators

Aggressive SM (organ dysfunction related to mast cell infiltration)

Associated with hematological neoplasm (organ dysfunction related to mast cell infiltration)

Mast cell leukemia (organ dysfunction related to mast cell infiltration)

Smoldering SM (No signs of aggressive disease but a high burden of mast cells.)
### Cutaneous Mastocytosis

Mechanical irritation may cause reddening and urticarial swelling of the lesions = Darier’s sign

<table>
<thead>
<tr>
<th></th>
<th>UP</th>
<th>DCM</th>
<th>Mastocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Red-brown to yellow maculopapular lesions</strong></td>
<td><strong>Diffuse skin infiltration with blistering erosions and crusts</strong></td>
<td><strong>One or several brown-red plaques or nodular lesions 4-5 cm in diameter</strong></td>
</tr>
</tbody>
</table>

**Figure 1.** Wheal formation in childhood UP.

**Figure 2.** Blistering typically presenting in DCM.
Systemic mastocytosis

WHO: 1 major and 1 minor OR 3 minors

**Major:**
Multifocal dense MC infiltrates (>15 cells in aggregates) detected in bone marrow and/or extracutaneous organs

**Minor:**

a. In a Bx for bone marrow or extracutaneous organs > than 25% of MC have a spindle shape or abnormal morphology / are immature in morphology

b. C-KIT 816 point mutation in bone marrow / blood / other extracutaneous site

c. MC in in bone marrow / blood / other extracutaneous site express CD2 and/or CD25 in addition to normal MC markers.

d. Tryptase > 20ng/ml


A compact infiltrate of round mast cells. Note the strong annular expression of CD25 by all the mast cells indicating an atypical immunophenotype in a case of D816V positive systemic mastocytosis.
Children vs adults

• In adults – Up to 50% of cases with apparent skin-limited mastocytosis may have a clonal BM mast cell infiltrate (without meeting WHO criteria of systemic forms).

• The diagnosis is more challenging in cases with no skin involvement (20% of ISM cases) and should be suspected when there are recurrent, unexplained anaphylaxis, flushing, osteoporosis, gastrointestinal ulceration or chronic abdominal cramps.

Greenberger and Metcalfe . JACI IP Apr 2019
**BIOMARKERS**

- Biopsy: The dermal mast cell infiltrate is revealed by (immuno)staining with toluidine blue, tryptase, or c-Kit/CD117, which reveals an average four- to five-time increase in spindled mast cells in the dermis.

- Analysis of DNA from lesional skin reveals \textit{KITD816V} in most adult cases but in less than half of pediatric cases.

- Full diagnostic testing including BM biopsy should be considered in any patient in whom SM is strongly suspected even in the absence of skin lesions.
### Diagnosis: Supportive lab tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Peak from symptoms</th>
<th>persists</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptase</td>
<td>60–90 min (ideal for measurement)</td>
<td>6 hours</td>
<td>No specific handling</td>
</tr>
<tr>
<td>Histamine</td>
<td>5–10 min</td>
<td>1 hour</td>
<td></td>
</tr>
</tbody>
</table>
| 24-h urinary histamine
  metabolites (N-methylhistamine) |                     |          |                                                   |
| PAF (PLT activating factor) |                     |          |                                                   |

- **Tryptase**
  - Peak from symptoms: 60–90 min (ideal for measurement)
  - Persist: 6 hours
  - Comment: No specific handling

- **Histamine**
  - Peak from symptoms: 5–10 min
  - Persist: 1 hour

- **24-h urinary histamine metabolites (N-methylhistamine)**
  - persists: up to 24 h after the onset of the event

- **PAF (PLT activating factor)**
  - The half-life of PAF is short, ranging from 3 to 13 minutes, because of its rapid inactivation by the enzyme PAF-AH
  - Requires special handling, increased in hypoxia

- Using cutoff of 400 pg/mL as the upper limit of normal, PAF levels were elevated in 26 (63%) of allergic patients but in no controls.

References:
- P. Lieberman. Allergy Frontiers: Diagnosis and Health Economics. 2009
Tryptase

• The appropriate time to measure released tryptase during MC activation events such as anaphylaxis (30-120 minutes after the development of symptoms) differs from that for measuring released histamine that peaks after 5 to 10 minutes.

• Increased tryptase defined as - tryptase level exceeded the published threshold of 2ng/ml + 1.2 x (baseline or post-reaction tryptase level).
Indications for bone marrow to R/O systemic mastocytosis:

• 1. Patients with idiopathic anaphylaxis (IA) with basal tryptase of 11.4mcg/ml or more.
• 2. An adult with UP and peripheral blood testing positive for KIT D816 mutation,
• 3. An adult with unexplained hepatosplenomegaly, osteoporosis with basal tryptase of 11.4mcg/ml or more.
Mastocytosis and venom allergy

- Two large studies reported that anaphylactic reactions to hymenoptera venom occur in 6-27% of adults mastocytosis, mostly systemic mastocytosis.

- Hymenoptera stings played no role in eliciting anaphylaxis in children with mastocytosis.

- Only one case of anaphylaxis to fire ant was reported in a 4-year-old girl with urticaria pigmentosa.

Table 2: Prevalence of clonal mast cell disease in patients with systemic reactions to hymenoptera venom, screened on the basis of elevated tryptase

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Tryptase ≥11.4 ng/ml [n (%)]</th>
<th>CMD</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haerberi et al. [5]</td>
<td>259</td>
<td>19 (7.3)</td>
<td>3 cutaneous mastocytosis</td>
<td>1</td>
</tr>
<tr>
<td>Dubois [6]</td>
<td>2275</td>
<td>92 (1.3)</td>
<td>22 systemic mastocytosis</td>
<td>1</td>
</tr>
<tr>
<td>Rueff et al. [4]</td>
<td>1102</td>
<td>106 (9.6)</td>
<td>21 cutaneous mastocytosis + 8 systemic mastocytosis</td>
<td>2.6</td>
</tr>
<tr>
<td>Bonadonna et al. [6**]</td>
<td>379</td>
<td>44 (11.6)</td>
<td>21 ISM + 9 MMAS</td>
<td>7.9</td>
</tr>
<tr>
<td>Potier et al. [31*]</td>
<td>138</td>
<td>22 (15.9)</td>
<td>1 cutaneous mastocytosis + 5 systemic mastocytosis</td>
<td>4.4</td>
</tr>
<tr>
<td>Guenova et al. [32?]</td>
<td>274</td>
<td>30 (10.9)</td>
<td>1 cutaneous mastocytosis + 3 ISM</td>
<td>1.5</td>
</tr>
</tbody>
</table>

CMD, clonal mast cells disease; ISM, indolent systemic mastocytosis; MMAS, Monoclonal Mast Cell Activation Syndrome.

* Bone marrow evaluation not performed.

** Screening with urinary Histamine metabolite.

† Evaluation of CD25/CD2 mast cell coreexpression and c-Kit mutation not performed or reported.
Fig. 1. Incidence of HVA in different variants of systemic mastocytosis (SM) and in monoclonal mast cell activation syndrome (MMAS) in our series of 434 patients. No patient initially presenting with hymenoptera anaphylaxis progressed to ASM; however, 1 patient with ISMs(−) and HVA developed a chronic myeloid leukemia and 1 patient with MMAS developed a myelofibrosis after 4.5 and 7 years from mastocytosis diagnosis, respectively. ISMs(−): indolent systemic mastocytosis without skin lesions. ISMs(+) : indolent systemic mastocytosis with skin lesions. ASM: aggressive systemic mastocytosis. ISM-AHNMD: indolent systemic mastocytosis-associated clonal hematological non-mast cell disease.

ISMs(-): indolent systemic mastocytosis without skin involvement

HVA-hymenoptera venom allergy
Mastocytosis , venom allergy, tryptase

• Basal serum tryptase was measured in 259 Hymenoptera venom-allergic patients (158 honey bee, 101 Vespula).

• 7% (19/259) patients had an elevated basal serum tryptase.

• Evidence of cutaneous mastocytosis (by skin biopsy) was present in minority of these [3 of 16 patients (18.8%)].

• Sting reaction severity increased with increased age and baseline tryptase levels (P = 0.001 and P = 0.0003, respectively) mainly in levels more than 5mg/l.

• Measuring sBT is a simple and inexpensive test, and routine measurement in patients with SAR to Hymenoptera stings should become part of common medical practice.

• Basal serum tryptase levels increase continuously with age and being an indicator for either increased mast cell load or reactivity.

Mastocytosis and tryptase

• Assessment of sBT is widely considered a useful screening test for mastocytosis in patients with SAR after hymenoptera stings.

• Some cases of systemic mastocytosis and especially with only cutaneous mastocytosis may present values less than 11.4mg/l.

• Elevated sBT may be found also in other conditions:

- Onchocerciasis—river blindness
- Chronic urticaria
- Chronic renal failure
- Haematologic diseases
Mastocytosis and venom- diagnosis of culprit

• In patients with venom anaphylaxis, sensitization can be detected by serology or skin tests

• The most common sensitivity in those with clonal mast cell disorder is to vespidea (due to more portent mast cell activators compared to honey bee)

• In some pts with mastocytosis venom specific IgE can not be detected potentially due to increased absorption of systemic IgE or due to non-IgE mediated degranulation of mast cells (BAT tests can be useful)

Mastocytosis and venom- indications for bone marrow (BM) biopsy

- Pts with venom allergy are recommended to have BM biopsy when serum tryptase is more than 20mcg/l or if there are signs or symptoms of systemic mastocytosis.

- About a third of pts with venom allergy and clonal mast cell disorder have basal tryptase less than 20 and it had been suggested that the cut off should be lowered to 11.4.

- Should consider BM also in cases with negative allergy tests / frequent systematic reactions to VIT

Mastocytosis and venom- treatment – Controversy

- **Con**: Some indicate that these are not IgE mediated and that side effects are frequent in VIT for these patients.

- **Pro**: VIT usually well tolerated and efficacious.

- **Case reports** support use of omalizumab prophylactically in patients with mastocytosis who were not able to reach maintenance.

Mastocytosis and VIT- treatment length and dose

• In most venom allergy cases – 5 years of VIT are recommended but in those with mastocytosis and venom induced anaphylaxis – there were reports on 3 fatalities after stopping VIT – and hence it is recommended to continue for life.

• In some cases that present with reactions once maintenance is achieved it is recommended to increase the dose to 200mcg and more.

Natural resolution (2001-2016)

229 articles were identified for resolution

217 articles excluded as they did not meet search criteria

12 articles were included in qualitative synthesis

5 articles evaluated rate of complete resolution
Natural resolution

• Complete pooled resolution rate for mastocytoma was 10% per year (95% CI: 4.8%, 15.1%)
• Resolution rate for urticarial pigmentosa was 1.9% per year (95% CI: −0.5%, 4.3%).
• Systemic mastocytosis subtypes did not show evidence of complete resolution in the studies reviewed.
Prevention of flares

• Common triggers to avoid: heat, changes in temperature, pressure, cold, or rubbing, some forms of exercise, emotions, stress, sleep deprivation.

• Drugs: opiates, NSAIDs, succinylcholine, and agents with tetrahydroisoquinoline (THIQ) motifs such as atracurium, rocuronium, quinolones that may activate MCs through non-IgE MRGPRX2 receptors.

• Alcohol (Ethanol increases the number of total and degranulated mast cells).

• Hymenoptera venoms.

Prevention of flares during surgery

- Particular attention needs to be paid at times of surgery, invasive procedures, radiological use of contrast media, vaccinations, and dental procedures.

- Premedication regimes have been used with a combination of anti-H1 and anti-H2 histamine receptor medications, an LT receptor blocker and 0.5 mg/kg of prednisone for major procedures and anti-H1 and anti-H2 histamine receptor medications for minor procedures.

Management of skin symptoms - mastocytosis

- Antihistamines

- Leukotriene receptor blockade.

- Inhibition of mediator synthesis (aspirin, zileuton)- There is no reason to avoid aspirin or other NSAIDs once a diagnosis of SM or MCAD has been made if the patient has tolerated these medications previously.

- 90% of patients will tolerate aspirin that will inhibit PGD2 formation.

- Inhibition of mediator release (sodium cromolyn) - 100 mg daily and escalate in 8 weeks to 800 mg divided in 200 mg 4 times daily, on an empty stomach before meals and at bed time (side effects – headache, constipation)

- Anti-IgE therapy.

- Acute episodes of mast cell activation require epinephrine.

- Prolonged episodes may be addressed with corticosteroids.

Results in cutaneous treatment options

• Antihistamines are the most commonly used as treatment of UP
  • Clinical results varied from complete resolution of symptoms (mainly pruritus) to no improvement

• Topical and oral corticosteroids were used in DCM and mastocytoma
  • Rapid regression and remission was observed when oral steroids were used in DCM
  • Complete resolution and plaque regression was observed with topical steroids in mastocytoma

• Phototherapy was used for UP and DCM
  • Improvement of pruritus but persistent cutaneous lesions in UP
  • Diminished dermographism and disappearance of skin thickening in DCM
**Results for systemic MC treatment options**

- Most commonly used biologics: imatinib and omalizumab (*KIT* mutation D816V, usually present in adult cases of SM, confers resistance against imatinib)

- Substantial improvement of SM with Omalizumab was recently observed

- Cladribine (purine analog with activity against both resting and actively dividing cells.), the most commonly used chemotherapy in SM, was reserved for more serious SM subtypes

- Allogeneic hematopoietic stem cell transplant (Allo-HCT) was the only surgical treatment used for SM patients

- Therapies found were purely symptomatic with none completely treating the disease
<table>
<thead>
<tr>
<th>Organ system involved</th>
<th>Disorders with symptoms that mimic mast cell activation</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Carcinoid, pheochromocytoma, thyrotoxicosis, medullary thyroid carcinoma, insulinima</td>
<td>5-HIAA in the urine and urinary metanephrines ((metanephrines, vanillylmandelic acid) ) chromogranin A in blood</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Labile HTN, pulm edema, syncope, orthostatic hypotension, paroxysmal arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>POTS, autonomic neuropathy, migraines, seizures, CVA</td>
<td></td>
</tr>
<tr>
<td>Pharmacologic</td>
<td>Withdrawal of adrenergic inhibitor, MAO interactions, serotonergic syndrome, drug use, chlorpropamide-alcohol flush, vancomycin red man syndrome</td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Common flushing, familial flushing, hyper/hypohydrosis</td>
<td></td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Somatization disorder, Hy</td>
<td></td>
</tr>
</tbody>
</table>
Hello, he is doing great, he has been a little itchy...so far seems great, crossing my fingers it keeps up!

- Xolair ® 150 mg SC monthly for 3 months.
- Asymptomatic, without disease flares within 1 month following treatment initiation.
- No substantial changes in tryptase/CD63
Mast cell activation syndrome
S

• 22 years old. Referred for assessment of allergies (MTL) symptoms - itching, flushing almost daily. No clear trigger. Since she is 3 years old.

• Reactine helps but does not control symptoms completely

• Limited to wheelchair since 2016 (fainting frequently)- since 3 years.

• Diagnosed with POTs.

• Diagnosed with Ehler Danlose.
Postural tachycardia syndrome (POTS)

- Excessive increase in heart rate with assumption of upright posture.
- The orthostatic tachycardia occurs in the absence of orthostatic hypotension and is associated with a >6-month history of symptoms that are relieved by recumbence.
- POTS can be treated with a combination of non-pharmacological approaches, a structured exercise training program, and often some pharmacological support (Garland EM, Celedonio JE, Raj SR.)
- Some POTS patients present with severe flushing in addition to their tachycardia and have an associated mast cell activation disorder.

https://zovon.com/latest-health-news/pots/
Ehlers-Danlos syndrome (EDS)

- Genetically heterogeneous group of heritable connective tissue disorders (HCTDs) defined by joint laxity, skin alterations, and joint hypermobility.

- The latest EDS classification recognized 13 subtypes

- cEDS is diagnosed mainly with:
  - skin hyperextensibility and atrophic scarring and general joint hyperlaxity and identification on molecular genetic testing

- Treatment – symptomatic


The link

• Ehlers-Danlos syndrome (EDS) and postural tachycardia syndrome (POTS) frequently coexist.

• The prevalence of EDS in those with POTS is 18% vs 0.02% prevalence of EDS in the general population.

• It has been described that individuals with these syndromes can even present symptoms compatible to MCADs, which could represent a new specific phenotype.


Results of pubmed search (till Apr 2019)


Results of search POTS and MACS

POTS AND mast cell activation

Search results
Items: 10

1. Increased prevalence of autonomic dysfunction due to postural orthostatic tachycardia syndrome in patients with eosinophilic gastrointestinal disorders.
   Huang KZ, Dellon ES.
   PMID:
   30851172
   Free Article

2. Selective Response to Omalizumab in a Patient With Concomitant ncMCAS and POTS: What Does it Teach us About the Underlying Disease?
   Kacar M, Denman S, Savic S.
   PMID:
   30073959
   Free Article

3. Postural orthostatic tachycardia syndrome and the potential role of mast cell activation.
   Doherty TA, White AA.
   PMID:
   30033040

Similar articles
Hypothesis for potential link

• MC are situated near nerve fibers, lymphatics, and blood vessels, as well as coupled with their ability to secrete potent mediators.

• MC dysregulation has been implicated in immediate and delayed hypersensitivity syndromes, neuropathies, and connective tissue disorders (CTDs).
A MCAS diagnosis requires:

1. Clinical symptomatology that is in keeping with the disorder

2. A transient, measurable increase in either serum tryptase or other markers of mast cell mediators

3. A response to agents that interfere with mast cell mediators (such as cetirizine)

Symptoms

• As a minimum
• The patient should have 4 of 6:
  • ADDFHM:
  • Abdominal pain
  • Dermatographism
  • Diarrhea
  • Flushing
  • Headache
  • Memory and concentrations difficulties

Unfortunately, some patients receive the diagnosis incorrectly or self-diagnose themselves and become persuaded that their symptoms are explained by MCAS. A bone marrow examination is not indicated unless there are associated physical findings and laboratory studies suggestive of a clonal mast cell disorder as discussed previously.

Greenberger and Metcalfe. JACI IP Apr 2019
Labs

- Elevated histamine metabolite (>230 µg methylhistamine/g creatinine) in a 4h urine sample started at the onset of a severe flushing spell.

- Increased tryptase above the patient's baseline value during symptomatic periods on more than two occasions, or baseline serum tryptase levels that are persistently above 15 ng/mL.

- Other assays are 24-h urine PGD2 or its metabolite, and 11-β-prostaglandin F2 alpha.

(Frei . Clin Rev Allergy Immunol. 2015 May 6.).
Pt says she “has MAS”

When asked was she diagnosed – she says “Yes it is in the differential diagnosis”

“My doctor told me not to do a tryptase level as it is unlikely to be consistent with MAS”

When tests for tryptase done during symptoms and at baseline mast cell levels were normal and the difference between levels was less than 2 (2.19 and 3)
Omalizumab therapy for mast cell-mediator symptoms in patients with ISM, CM, MMAS and MCAS

Richard Lemal, MD, Guillemette Fouquet, MD, Louis Terriou, MD, Mélanie Vaes, MD, Cristina Bulai Livideanu, MD, Laurent Frenzel, MD, PhD, Stéphane Barete, MD, PhD, Danielle Canioni, MD, Ludovic Lhermitte, MD, PhD, Julien Rossignol, MD, PhD, Michel Arock, PharmD, PhD, Patrice Dubreuil, PhD, Olivier Lortholary, MD, PhD, Olivier Hermine, MD, PhD
### Table 1. Patients’ characteristics.

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>N = 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years, median (range)</td>
<td>41 (2 – 87)</td>
</tr>
<tr>
<td>Age at omalizumab treatment, years, median (range)</td>
<td>48 (17 – 93)</td>
</tr>
<tr>
<td>Time from diagnosis to omalizumab treatment, median (range)</td>
<td>3 years (2 months - 37 years)</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

#### Disease classification in the whole cohort

<table>
<thead>
<tr>
<th>Primary MCAS (N=41)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indolent Systemic Mastocytosis (ISM), N (%)</strong></td>
<td>29 (52.7)</td>
</tr>
<tr>
<td>- KIT D816V mutation positive, N</td>
<td>23</td>
</tr>
<tr>
<td>- KIT D816V mutation negative, N</td>
<td>5</td>
</tr>
<tr>
<td>- KIT D816V mutation not evaluated</td>
<td>1</td>
</tr>
<tr>
<td><strong>Cutaneous Mastocytosis (CM), N (%)</strong></td>
<td>11 (20)</td>
</tr>
<tr>
<td>- KIT D816V mutation positive, N</td>
<td>3</td>
</tr>
<tr>
<td>- KIT D816V mutation negative, N</td>
<td>6</td>
</tr>
<tr>
<td>- KIT D816V mutation not evaluated</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Idiopathic MCAS (N=14)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mast Cell Activation Syndrome (MCAS), N (%)</strong></td>
<td>15 (27.3)</td>
</tr>
<tr>
<td>- KIT D816V mutation positive (=MMAS), N</td>
<td>1</td>
</tr>
<tr>
<td>- KIT D816V mutation negative, N</td>
<td>11</td>
</tr>
<tr>
<td>- KIT D816V mutation not evaluated</td>
<td>3</td>
</tr>
</tbody>
</table>
Symptoms score

- 1.5: Worsening of the symptom.
- 1: No change.
- 0.75: Slight improvement.
- 0.5: Substantial improvement.
- 0.25: Dramatic improvement.
- 0: Complete disappearance of the symptom.
Omalizumab treatment

- Dose of 150 mg every 2 weeks up to 150mg weekly.
- Median time to response was 6 months.
- Omalizumab was dramatically effective on all superficial and vasomotor symptoms and most GI symptoms
- One pt had laryngeal edema with omalizumab.
Findings

- Among all 55 pts 1 had a complete response and the majority (55%) had a major response – improvement of 50% or more
- 78% had some response for all and 70% among those with MAS

Table 2. Response rates.

<table>
<thead>
<tr>
<th></th>
<th>All patients (N=55)</th>
<th>Primary MCAS (N=41)</th>
<th>Idiopathic MCAS (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (N=41)</td>
<td>ISM (N=29)</td>
<td>CM (N=11)</td>
</tr>
<tr>
<td><strong>Best response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, N (%)</td>
<td>43 (78.2)</td>
<td>34 (82.9)</td>
<td>23 (79.3)</td>
</tr>
<tr>
<td>CR, N (%)</td>
<td>1 (1.8)</td>
<td>1 (2.4)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>MR, N (%)</td>
<td>30 (54.5)</td>
<td>22 (53.7)</td>
<td>16 (55.2)</td>
</tr>
<tr>
<td>PR, N (%)</td>
<td>12 (21.8)</td>
<td>11 (26.8)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>No response, N (%)</td>
<td>12 (21.8)</td>
<td>7 (17.1)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>5 (35.7)</td>
</tr>
<tr>
<td><strong>Response at last follow up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent ORR, N (%)</td>
<td>32 (58.2)</td>
<td>25 (61)</td>
<td>17 (58.6)</td>
</tr>
<tr>
<td>CR, N (%)</td>
<td>1 (1.8)</td>
<td>1 (2.4)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>MR, N (%)</td>
<td>23 (41.8)</td>
<td>17 (41.5)</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>PR, N (%)</td>
<td>8 (14.5)</td>
<td>7 (17.1)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>No persistent response, N (%)</td>
<td></td>
<td>23 (41.8)</td>
<td>16 (39)</td>
</tr>
<tr>
<td>No response, N (%)</td>
<td>12 (21.8)</td>
<td>7 (17.1)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Loss of response, N (%)</td>
<td>4 (7.3)</td>
<td>3 (7.3)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Intolerance, N (%)</td>
<td>3 (5.4)</td>
<td>3 (7.3)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Lost from follow-up, N (%)</td>
<td>4 (7.3)</td>
<td>3 (7.3)</td>
<td>3 (10.3)</td>
</tr>
</tbody>
</table>

Findings

• Median time to response was 2 months.

• At follow up the majority were on still on omalizumab.

• 1/3 had to increase dose to 300mg every 2 weeks.

• In 5% due to flare dose was changed to 150mg weekly with good control of symptoms.
• 16 YO girl with recurrent anaphylaxis.
• Severe abdominal pain, vomiting, diarrhea followed sometimes by itchiness and hives.
• 6-7 X/month, usually at night between 10-11 pm (2 hours after eating).
• The episodes seemed to occur in the context of her menstruation (a few days before, during or a few days after). Otherwise no clear triggers could be identified.
NB continued- work up

- Neg skin prick tests and specific IgE for common food allergens.
- Total IgE elevated: 4032 kU/L

- Tryptase levels were elevated during attacks (17.4 µg/L) and normal at baseline (3.4 µg/L).

- Undetectable levels of alpha-gal (Thomas Platts-Mill laboratory, University of Virginia, United States)

- cKIT 816 mutation was not detected in peripheral blood (Thomas Kristensen laboratory, Dept. of Pathology, Odense University Hospital, Denmark).

- Abdominal ultrasound: no abnormalities.

- Urine collection over 24 hours for 5HIAA and VMA was normal.

- A bone marrow biopsy: no abnormal mast cell infiltrates and normal staining for cKIT and tryptase.
Management initial

• Instructed to carry an Epipen auto-injector and we advised to begin treatment with Reactine 20 mg daily which did not improve her symptoms.
IA: Idiopathic anaphylaxis

- Idiopathic anaphylaxis is a diagnosis of exclusion and should be made only after extensive evaluation to exclude other potential causes of anaphylaxis and other diseases with similar manifestations.

- Classification of the disease is necessary to determine the appropriate treatment course for IA.

- Frequent episodes are defined as at least 2 episodes in the preceding 2 months or at least 6 episodes in the preceding year.

- In the last 26 years among 92 fatalities due to anaphylaxis, 6 were defined as idiopathic.

Anaphylaxis due to an unknown trigger vs IA

Table 3 Anaphylaxis triggers

<table>
<thead>
<tr>
<th>Type of anaphylaxis trigger</th>
<th>BCCH (n=346)</th>
<th>MCH (n=631)</th>
<th>Diff BCCH – MCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food trigger (%)</td>
<td>91.3 (88.7, 94.0)</td>
<td>82.4 (79.7, 85.3)</td>
<td>8.9 (4.5, 13.3)</td>
</tr>
<tr>
<td>Among all food-triggered reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PN</td>
<td>24.7 (20.1, 29.9)</td>
<td>19.0 (15.8, 22.7)</td>
<td>5.6 (−0.4, 11.7)</td>
</tr>
<tr>
<td>TNs</td>
<td>19.0 (14.9, 23.8)</td>
<td>16.0 (13.0, 19.5)</td>
<td>3.0 (−2.6, 8.6)</td>
</tr>
<tr>
<td>PN/TNs/nuts unclear</td>
<td>7.9 (5.3, 11.6)</td>
<td>6.5 (4.6, 9.1)</td>
<td>1.4 (−2.5, 5.3)</td>
</tr>
<tr>
<td>Milk</td>
<td>4.8 (2.8, 7.8)</td>
<td>6.7 (4.8, 9.3)</td>
<td>−2.0 (5.4, 14.5)</td>
</tr>
<tr>
<td>Egg</td>
<td>6.0 (3.8, 9.4)</td>
<td>7.9 (5.8, 10.6)</td>
<td>−1.9 (−5.6, 1.9)</td>
</tr>
<tr>
<td>Shellfish</td>
<td>1.9 (0.08, 4.3)</td>
<td>2.9 (1.7, 4.8)</td>
<td>−1.0 (−3.3, 1.4)</td>
</tr>
<tr>
<td>Sesame</td>
<td>2.2 (1.0, 4.7)</td>
<td>1.9 (1.0, 3.6)</td>
<td>0.2 (−2.0, 2.6)</td>
</tr>
<tr>
<td>Fish</td>
<td>2.5 (1.2, 5.1)</td>
<td>2.7 (1.5, 4.6)</td>
<td>−0.2 (−2.5, 2.2)</td>
</tr>
<tr>
<td>Kiwi</td>
<td>0.6 (0.1, 2.5)</td>
<td>0.4 (0.01, 1.5)</td>
<td>0.2 (−1.0, 1.5)</td>
</tr>
<tr>
<td>Soy</td>
<td>0</td>
<td>0.6 (0.1, 1.8)</td>
<td>−0.6 (−1.5, 0.3)</td>
</tr>
<tr>
<td>Wheat</td>
<td>1.9 (0.08, 4.3)</td>
<td>0.8 (0.2, 2.1)</td>
<td>1.1 (−0.8, 3.1)</td>
</tr>
<tr>
<td>Nonfood triggers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venom</td>
<td>0.9 (0.0, 3.6)</td>
<td>1.4 (0.0, 4.3)</td>
<td>−0.6 (−2.1, 1.0)</td>
</tr>
<tr>
<td>Drug</td>
<td>2.0 (0.0, 4.7)</td>
<td>3.6 (0.9, 6.5)</td>
<td>−1.6 (−3.9, 0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>0.9 (0.0, 3.6)</td>
<td>2.1 (0.0, 5.0)</td>
<td>1.2 (−2.9, 0.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4.9 (2.3, 7.6)</td>
<td>10.5 (7.7, 13.4)</td>
<td>−5.5 (−9.1, 2.0)</td>
</tr>
</tbody>
</table>

Abbreviations: BCCH, British Columbia Children’s Hospital; MCH, Montreal Children’s Hospital; Diff, difference; CI, confidence interval; PN, peanut; TNs, tree nuts.

- Children compared to adults were more likely to receive treatment with epinephrine either inside or outside the hospital (74.8% vs 50.7%).
- Assessment by allergist to uncover a potential was more common in children (80%) adults (50%).
Anaphylaxis due to an unknown trigger vs IA

- Of those assessed almost in 40% of pediatric cases and 20% of adult cases a trigger was identified.
- Tests for tryptase, exercise, alpha gal, bone marrow are rarely done.
- Almost a third experienced a future episode.
Tx

- Frequent episodes: Continuous prednisone at a dose of 40-60 mg, antihistamine (e.g. cetirizine 10 mg) and sympathomimetics (e.g. albuterol) with gradual taper.

- Patients with infrequent episodes are treated when episodes occur with epinephrine, antihistamines and oral steroids.

- More recently the use of omalizumab was suggested to benefit patients with IA.
NB

- Treatment with Omalizumab 300 mg monthly was started and she has been in remission since then, for one year.
- Stopped omalziumab March 2017

Apr 26 2017: This is to inform you that I, unfortunately, suffered from a reaction late on Tuesday night and that I had to use my epipen. I went to the emergency (RVH) thereafter. The symptoms were the same as always (itchy palms, rashes, vomiting..etc). Should we restart the Xolair (My last injection was in mid march)?

- Treatment restarted with no new episodes
Side effects for omalizumab

• Anaphylaxis is rare.
• Most cases (~70%) of susp anaphylaxis occurred within the first 3 dose
• Risk factor: prior history of anaphylaxis unrelated to omalizumab
• More than half of the anaphylactic events happened within 60 minutes of omalizumab administration

Case

- A 17-year-old boy, who was referred to the Allergy-Immunology clinic, due to CU (>10 yrs) poorly controlled with high doses of anti-histamines (4 times the standard dose).
- Physical examination revealed diffuse hives and clear dermographism.
- UAS7 of 28.
- Borderline high tryptase (13.9 microgram/L, normal 0-13.5) on 3 repeated blood tests.
- Skin biopsy did not reveal vasculitis and staining for mast cell markers revealed normal mast cell morphology.
- Family history: father with daily pruritus and elevated tryptase.
- Two healthy brothers one with elevated tryptase. Sister assessed for ketotic hypoglycemia and pain crisis.
Familial Hyper-tryptasemia and Chronic Urticaria
Diagnosis and management challenges

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2. Division of Allergy, Immunology and Dermatology, Montreal Children’s Hospital, Montreal, QC, Canada.
3. Division of Dermatology, McGill University, Montreal, QC, Canada.

Abstract GUF meeting. Berlin 1017
Background

- Hereditary alpha tryptasemia syndrome (HATS) is characterized by high blood level of alpha tryptase and affects multiple organ systems.
- Affects 6% of the population
- Studies suggest that HATS is associated with cases of chronic urticaria (CU).
- The mode of inheritance is autosomal dominant, the expressivity and penetrance is unclear.
- Symptoms include flushing and pruritus, dysautonomia, functional gastrointestinal symptoms, chronic pain, and connective tissue abnormalities.
Genetics and management

- Assessment of number of copies of alpha and beta tryptase alleles on chromosome 16.
- Alpha tryptase is coded by TPSAB1 gene and beta tryptase is coded by TPSB2 and by TPSAB1 genes.
- The normal result is a combination of alpha and beta tryptase that adds up to 4.
- The index patient a brother and father had extra allelic alpha tryptase copies (3 copies of alpha and 2 copies of beta tryptase).
- Mother did not share this mutation.
- The patient was treated with Omalizumab 300 mg monthly subcutaneous injection and experienced complete resolution of hives (UAS7 of 0).
Conclusion

• Mast cell disorder are a challenging diagnosis

• High morbidity and risk of mortality

• Omalizumab is likely to benefit various pathologies in which Mast cell play a major role but large scale studies are required to establish its‘ effect and safety .

• Future studies exploring modified omalizumab protocols the resistant cases and the use in young children are required.

• We are currently establishing a registry that will aim to assess clinical characteristics management and natural history of mastocytosis – Please contact us to help improve the management of patients with mast cell disorders .
Thank you

Merci