

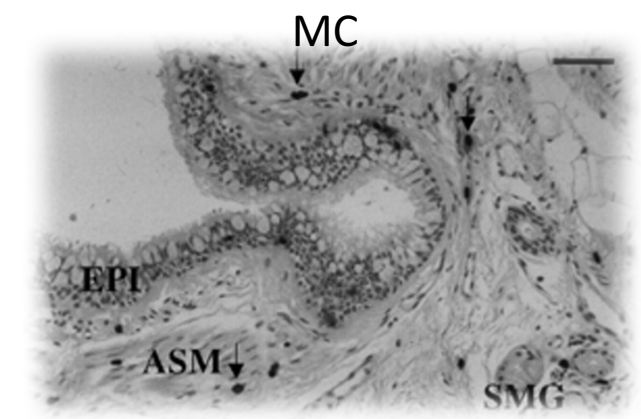
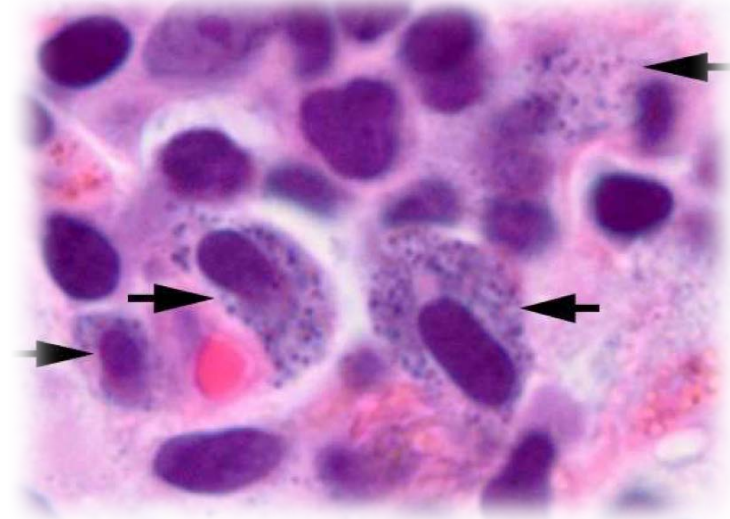


# Mast cell disorders- more than just hives

Dr Moshe Ben-Shoshan, MD, MSc  
Associate professor  
Division of allergy immunology and dermatology  
Department of Pediatrics  
Montreal Children's Hospital

# Objectives

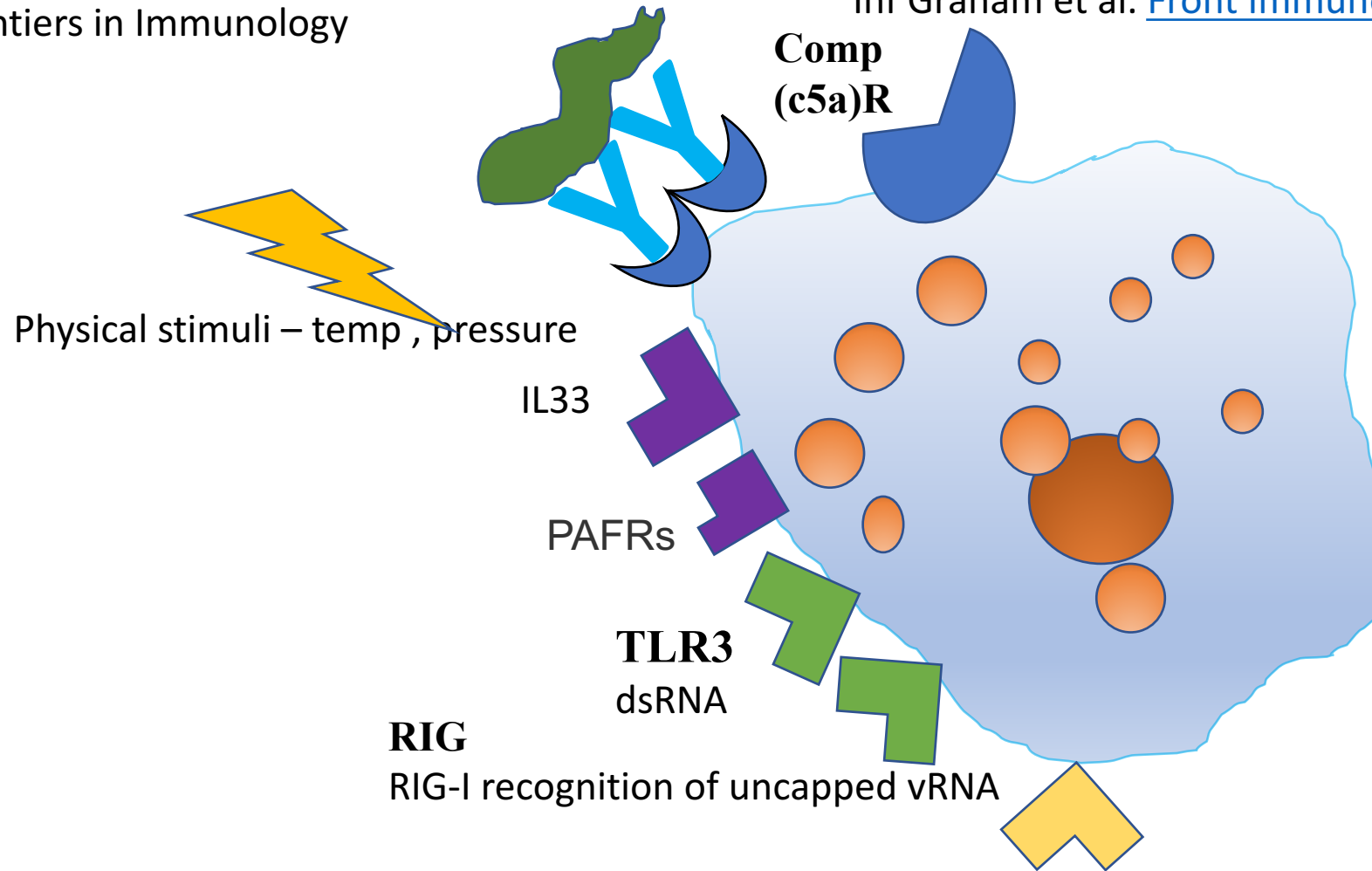
- 1. To discuss the role of mast cell in disease
- 2. To present the main mast cell disorders : classification and diagnosis (mastocytosis , mast cell activation syndrome , idiopathic anaphylaxis )
- 3. To discuss management and our call for a new registry .



# 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

N.G. Carroll, S. Mutavdzic, A.L. James  
 European Respiratory Journal 2002



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

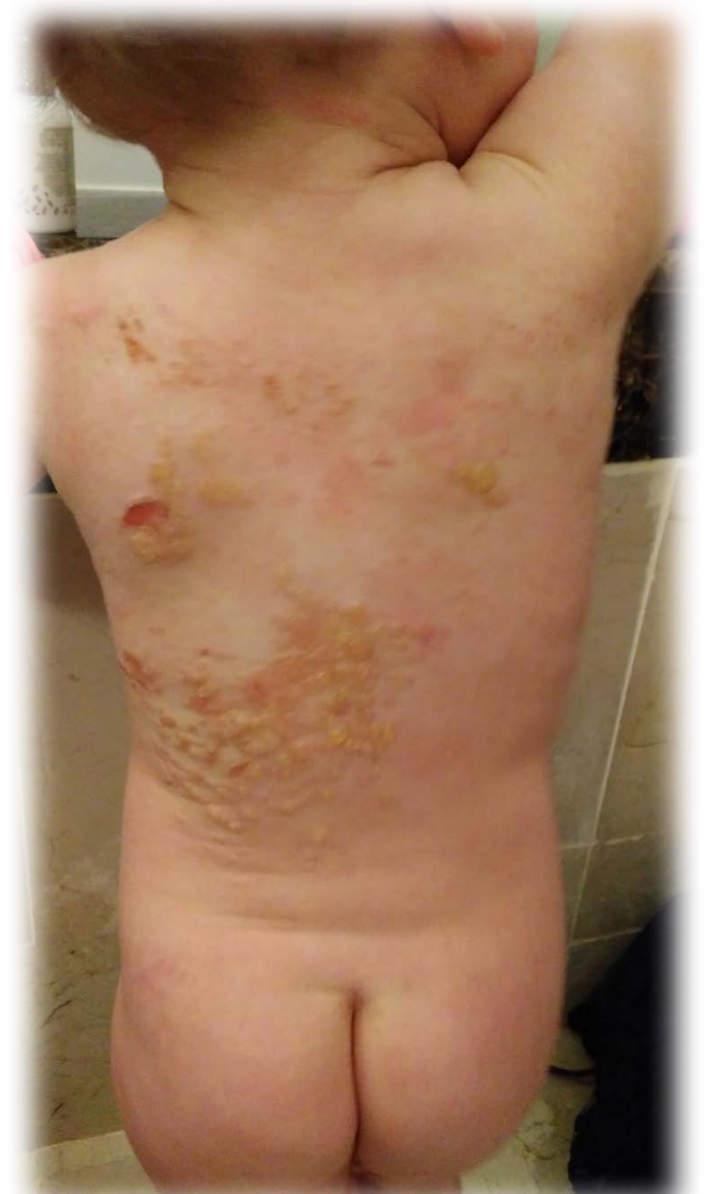
**Lipid :Eicosanoides**  
**(minutes ) :**  
**PGD2, PGF2**  
**LT PAF**

**Cytokines , chemokines**  
**GF(hours ) : TNFa, 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)

# PP

- 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.
- Trypase =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.



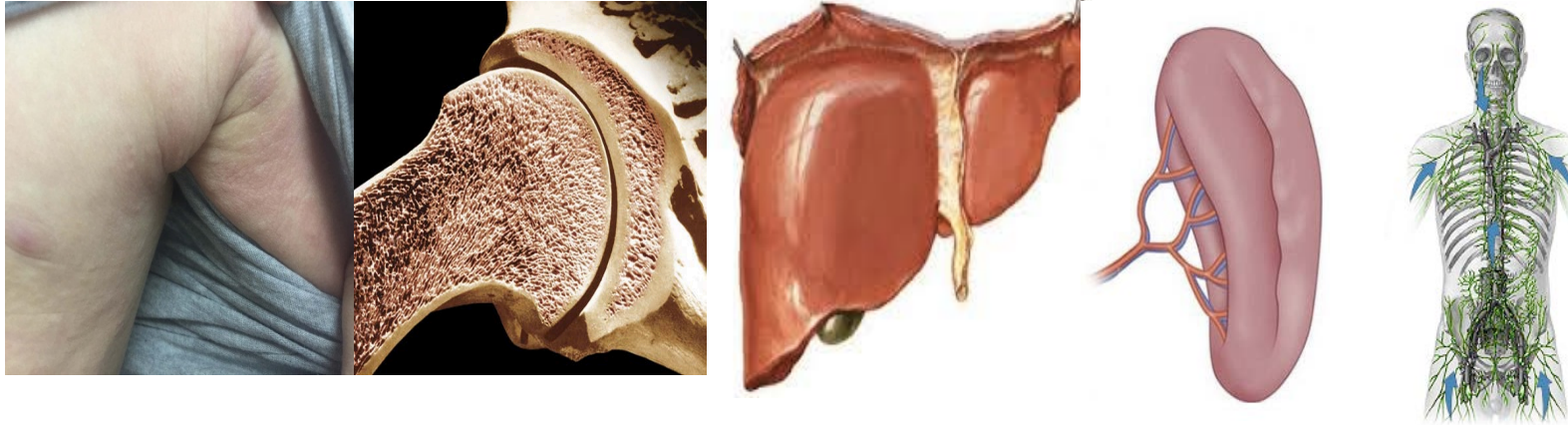
Concise report

Effective management of severe cutaneous mastocytosis in young children with omalizumab (Xolair®)

J. D. M. Hughes,<sup>1</sup> T. Olynyc,<sup>2</sup> H. Chapdelaine,<sup>3</sup> L. Segal,<sup>4</sup> B. Miedzybrodzki<sup>5</sup> and M. Ben-Shoshan<sup>5,6</sup>

CED  
Clinical and Experimental Dermatology

# 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

# Cutaneous Mastocytosis(CM)

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

**Diffuse Cutaneous Mastocytosis**

**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,)

**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.

# Cutaneous Mastocytosis

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

## UP

- Red-brown to yellow maculopapular lesions



## DCM

- Diffuse skin infiltration with blistering erosions and crusts



## Mastocytoma

- One or several brown-red plaques or nodular lesions 4-5 cm in diameter





# Systemic mastocytosis

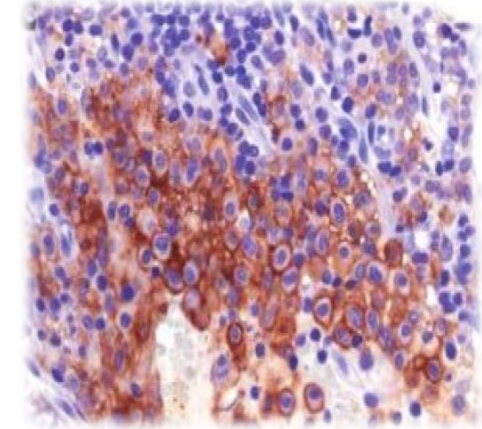
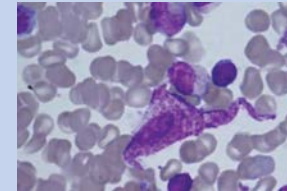
WHO: 1 major and 1 minor OR 3 minors

## Major :

Multifocal dense MC infiltrates (>15 cells in aggregates) detected in bone marrow and/ other extracutaneous organs

## Minor:

- In a Bx for bone marrow or extracutaneous organs > than 25% of MC have a spindle shape or abnormal morphology / are immature in morphology
- C-KIT 816 point mutation in bone marrow / blood / other extracutaneous site
- MC in in bone marrow / blood / other extracutaneous site express CD2 and/ CD25 in addition to normal MC markers.
- Tryptase > 20ng/ml



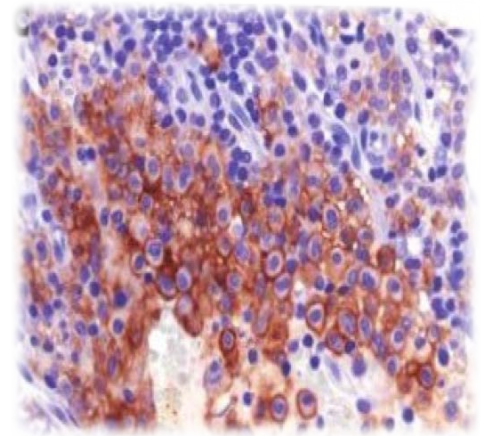
A compact infiltrate of round mast cells. Note the strong annular expression of CD25 by all the mast cells indicating an atypical immunophenotype in a case of D816V positive systemic mastocytosis

# 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.



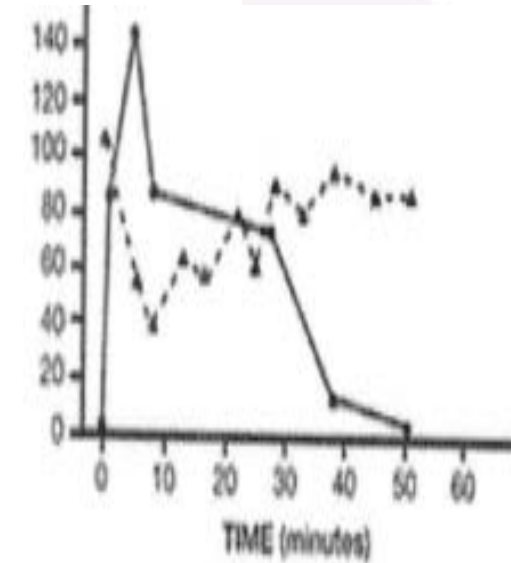
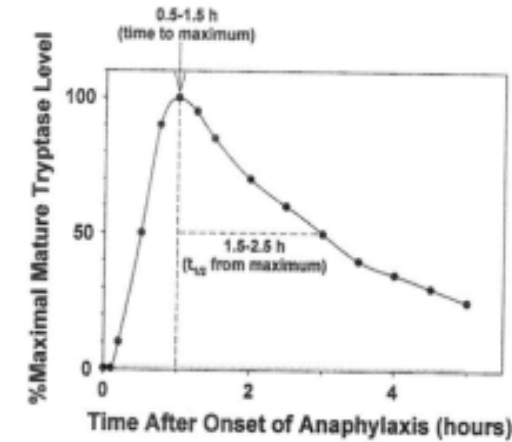
# BIOMARKERS



- 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 *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

	Peak from symptoms	persists	Comment
<b>Tryptase</b>	60–90 min (ideal for measurement)	6 hours	No specific handling
<b>Histamine</b>	5–10 min	1 hour	
<b>24-h urinary histamine metabolites</b> ( <i>N</i> -methylhistamine)		up to 24 h after the onset of the event	
<b>PAF ( PLT activating factor)</b>		The half-life of PAF is short, ranging from 3 to 13 minutes, because of its rapid inactivation by the enzyme PAF-AH	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



P. Lieberman. *Allergy Frontiers: Diagnosis and Health Economics*. 2009

Vadas et al. *J Allergy Clin Immunol*. 2013 Jan;131(1):144-9. G Paraskevopoulos. *Eur Ann Allergy Clin Immunol* VOL 45, N 2, 52-55, 2013

•Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am* 2006; 26(3):451-63.

Spring J, Weingarten TN, Schwartz LB. *Anesthesiology* 2015; 122(3):713-4.

Requires special handling

# 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  $2\text{ng/ml} + 1.2 \times$  (baseline or post-reaction tryptase level).

## **Tryptase levels in children presenting with anaphylaxis: Temporal trends and associated factors**

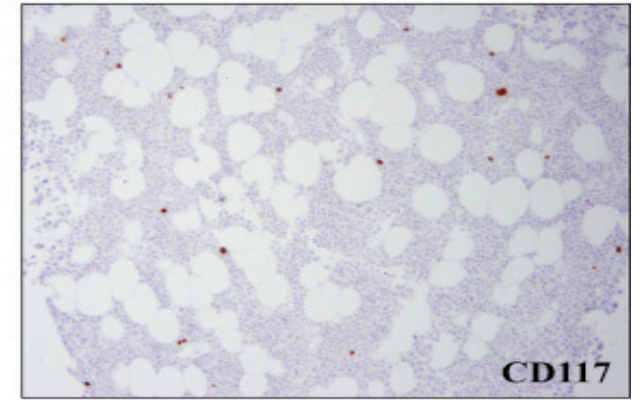
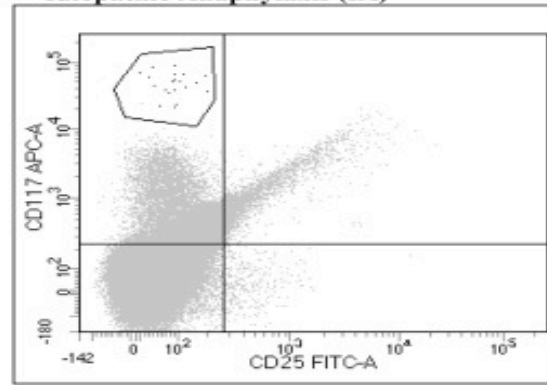


Sarah De Schryver, MD,<sup>a</sup> Michelle Halbrich, MD,<sup>b</sup> Ann Clarke, MD, MSc,<sup>c</sup> Sebastien La Vieille, MD,<sup>d</sup> Harley Eisman, MD,<sup>e</sup> Reza Alizadehfar, MD,<sup>a</sup> Lawrence Joseph, PhD,<sup>f</sup> Judy Morris, MD, MSc,<sup>g</sup> and Moshe Ben-Shoshan, MD, MSc<sup>a</sup>  
*Montreal, Quebec, Winnipeg, Manitoba, Calgary, Alberta, and Ottawa, Ontario, Canada*

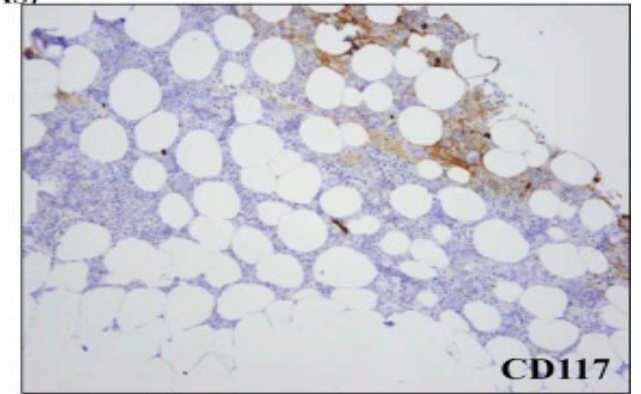
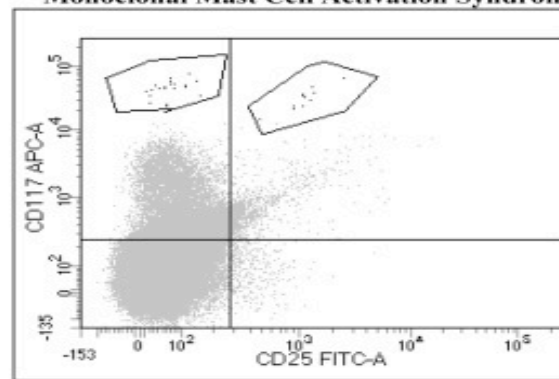
# Indications for bone marrow to R/O systemic mastocytosis:

- 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.

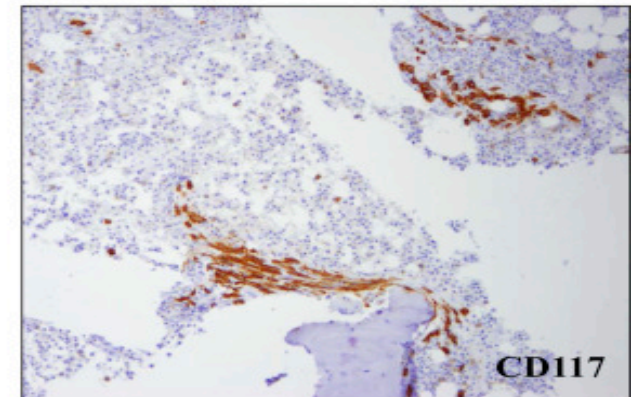
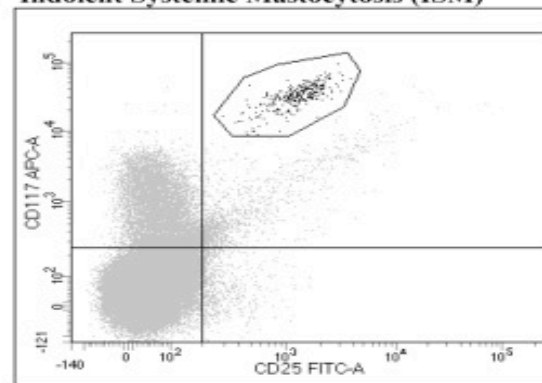
**A Idiopathic Anaphylaxis (IA)**



**B Monoclonal Mast Cell Activation Syndrome (MMAS)**



**C Indolent Systemic Mastocytosis (ISM)**



# 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**

Reference	Patients	Tryptase $\geq 11.4$ ng/ml [n (%)]	CMD	Percentage
Haerberli <i>et al.</i> [5]	259	19 (7.3)	3 cutaneous mastocytosis <sup>a</sup>	1
Dubois [3]	2375	32 <sup>b</sup> (1.3)	22 systemic mastocytosis	1
Rueff <i>et al.</i> [4]	1102	106 (9.6)	21 cutaneous mastocytosis + 8 systemic mastocytosis <sup>d</sup>	2.6
Bonadonna <i>et al.</i> [9**]	379	44 (11.6)	21 ISM + 9 MMAS	7.9
Potier <i>et al.</i> [31*]	138	22 (15.9)	1 cutaneous mastocytosis + 5 systemic mastocytosis <sup>d</sup>	4.4
Guenova <i>et al.</i> [32*]	274	30 (10.9)	1 cutaneous mastocytosis + 3 ISM <sup>c,d</sup>	1.5

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

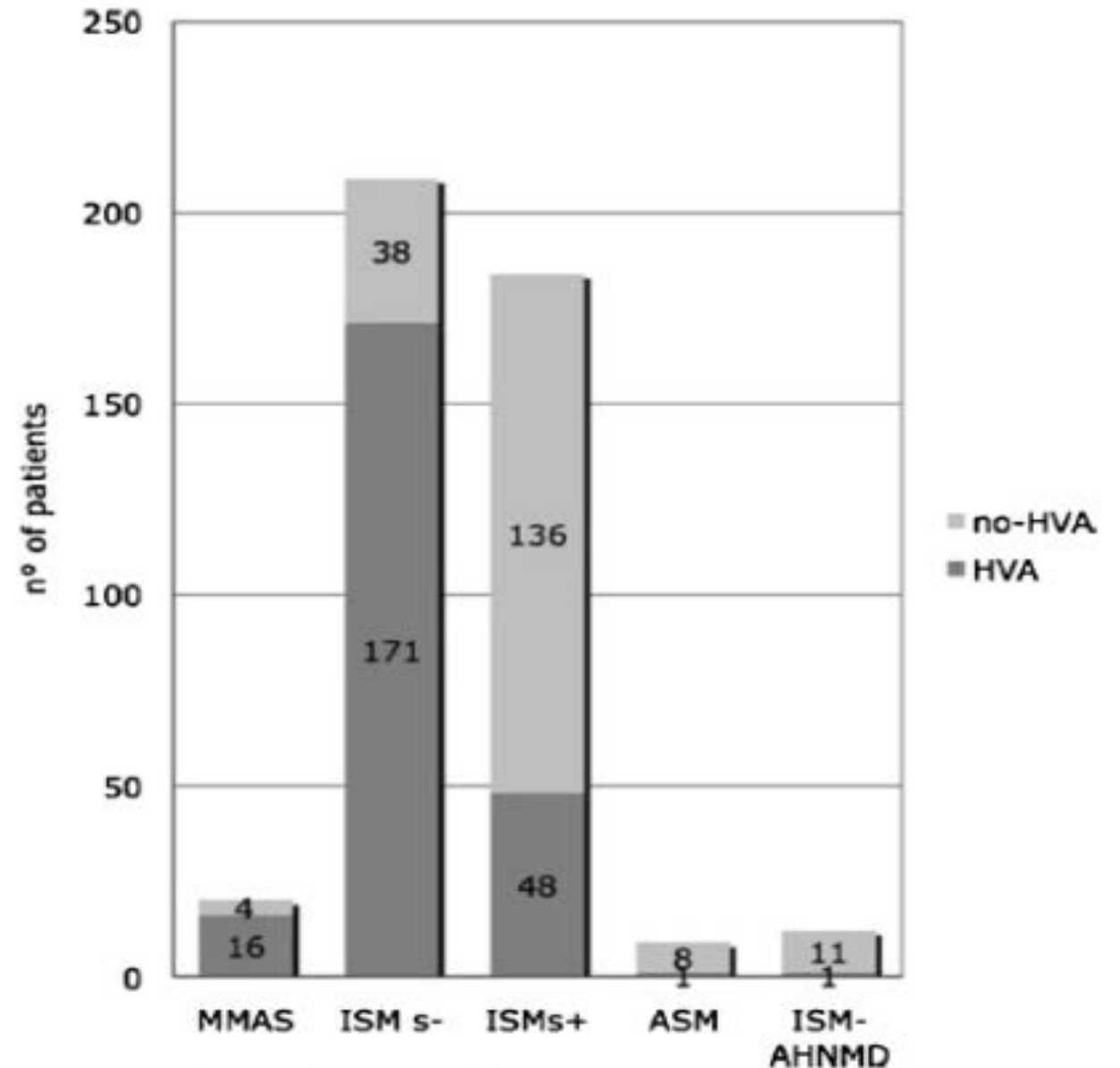
<sup>a</sup> Bone marrow evaluation not performed.

<sup>b</sup> Screening with urinary Histamine metabolite.

<sup>c</sup> Bone marrow evaluation performed if sBT higher than 15 ng/ml.

<sup>d</sup> Evaluation of CD25/CD2 mast cell coexpression 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

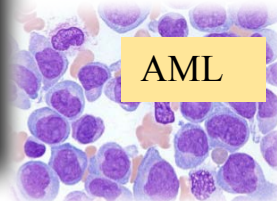
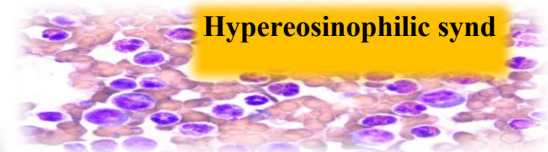


# Mastocytosis and tryptase

- 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:



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 potent 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 .

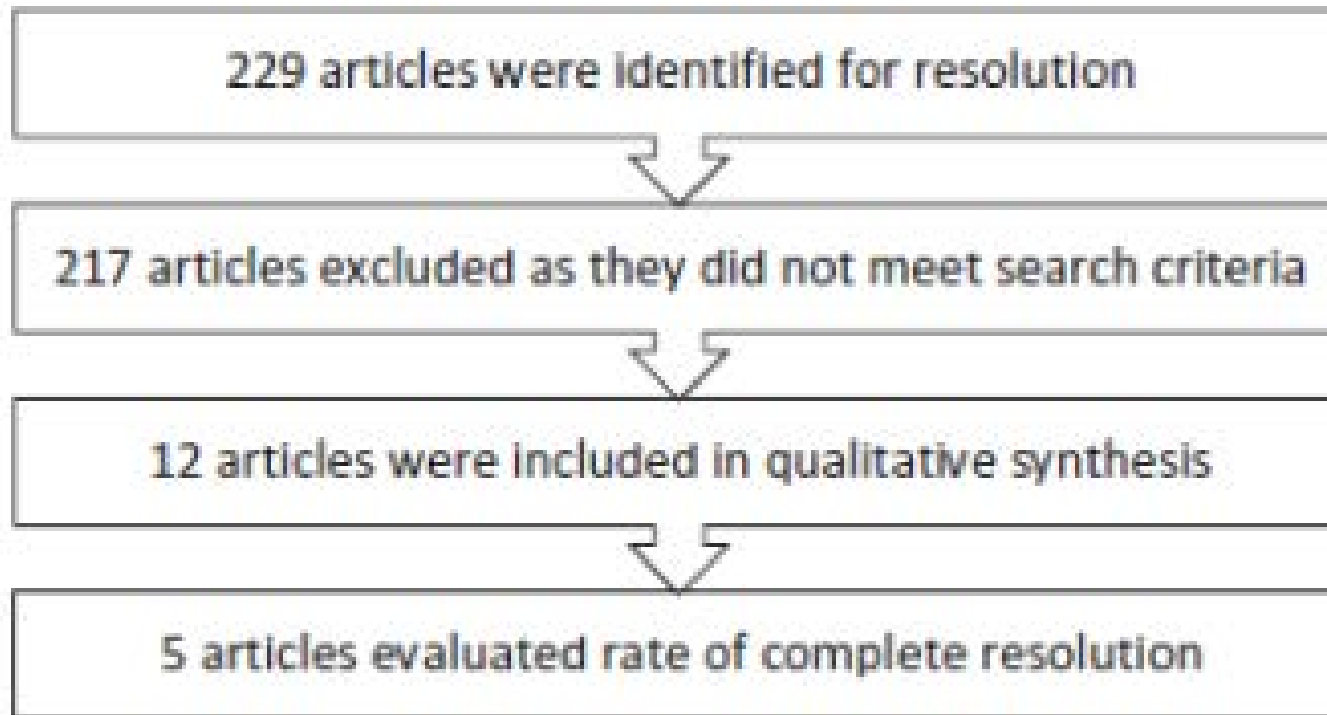
# Mastocytosis and VIT- treatment length and dose

- 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 history and treatment of cutaneous and systemic mastocytosis

Michelle Le<sup>a</sup>, Barbara Miedzybrodzki<sup>a</sup>, Tim Olynych<sup>b</sup>, Hugo Chapdelaine<sup>c</sup> and Moshe Ben-Shoshan<sup>a</sup>

# Natural resolution (2001-2016)



# 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.

**Generalized pruritus relieved by NSAIDs in the setting of mast cell activation syndrome**

Katrina Kesterson, MS<sup>a</sup>, Zachary Nahmias, MD<sup>b</sup>,

Castells M, Butterfield J.J Allergy Clin Immunol Pract.  
2019 Apr;7(4):1097-1106.

# 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



# Differential diagnosis

Organ system involved	Disorders with symptoms that mimic mast cell activation	comments
Endocrine	Carcinoid , pheochromocytoma , thyrotoxicosis, medullary thyroid carcinoma , insullinoma	5-HIAA in the urine ma and urinary metanephrines ((metanephrines, vanillymandelic acid) ) chromogranin A in blood
Cardiovascular	Labile HTN , pulm edema , syncope , orthostatic hypotension , paroxysmal arrhythmias	
Neurologic	POTS, autonomic neuropathy , migraines , seizures , CVA	
Pharmacologic	Withdrawal of adrenergic inhibitor , MAO interactions , serotonergic syndrome , drug use , chlorpropamide-alcohol flush, vancomycin red man syndrome	
Cutaneous	Common flushing , familial flushing , hyper/hypohydrosis	
Psychogenic	Somatization disorder , Hy	



Hello, he is doing great, he has been a little itchy...so far seems great, crossing my fingers it keeps up!

- Xolair<sup>®</sup>) 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***

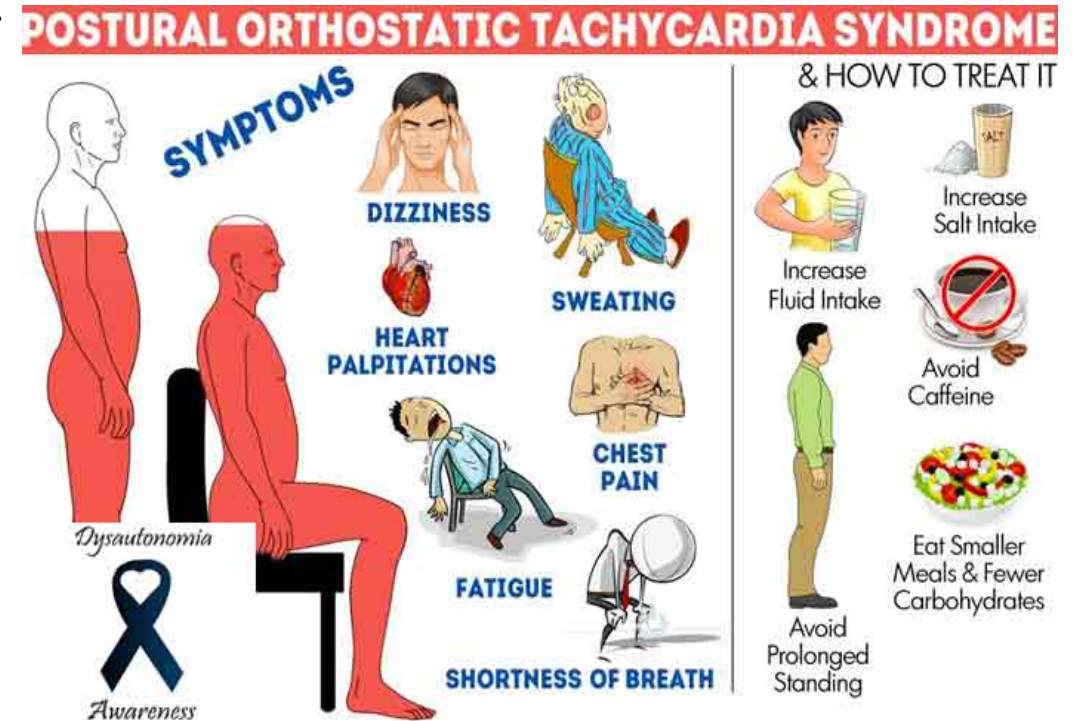


# S

- 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



<https://theheartysoul.com/eds-ehlers-danlos-syndrome/>

[Cortini et al. Arch Dermatol Res.](#) 2019 Mar 2.

Malfait F et al. In: Adam MP, Ardinger. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. 2007 May 29 [updated 2018 Jul 26].

# 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)

US National Library of Medicine National Institutes of Health

Search database PubMed

Search term

Ehlers-Danlos syndrome AND mast cell activation

Search

- [Create RSS](#)
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Items: 9

Select item 30851172 1.

[Increased prevalence of autonomic dysfunction due to postural orthostatic tachycardia syndrome in patients with eosinophilic gastrointestinal disorders.](#)

Huang KZ, Dellon ES.

J Gastrointest Liver Dis. 2019 Mar;28(1):47-51. doi: 10.15403/jgld.2014.1121.281.syd.

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Qureshi AA, Friedman AJ.

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[Chronic Fatigue Syndrome: From Chronic Fatigue to More Specific Syndromes.](#)

Blitshteyn S, Chopra P.

Eur Neurol. 2018;80(1-2):73-77. doi: 10.1159/000493531. Epub 2018 Oct 4.

# Results of search POTS and MACS

PubMed

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## POTS AND mast cell activation

### Search results

Items: 10

Select item 30851172  1.

[Increased prevalence of autonomic dysfunction due to postural orthostatic tachycardia syndrome in patients with eosinophilic gastrointestinal disorders.](#)

Huang KZ, Dellon ES.

J Gastrointest Liver Dis. 2019 Mar;28(1):47-51. doi: 10.15403/jgld.2014.1121.281.syd.

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Select item 30073959  2.

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Kacar M, Denman S, Savic S.

J Investig Allergol Clin Immunol. 2018 Aug;28(4):261-263. doi: 10.18176/jiaci.0251. No abstract available.

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[Postural orthostatic tachycardia syndrome and the potential role of mast cell activation.](#)

Doherty TA, White AA.

Auton Neurosci. 2018 Dec;215:83-88. doi: 10.1016/j.autneu.2018.05.001. Epub 2018 May 4. Review.

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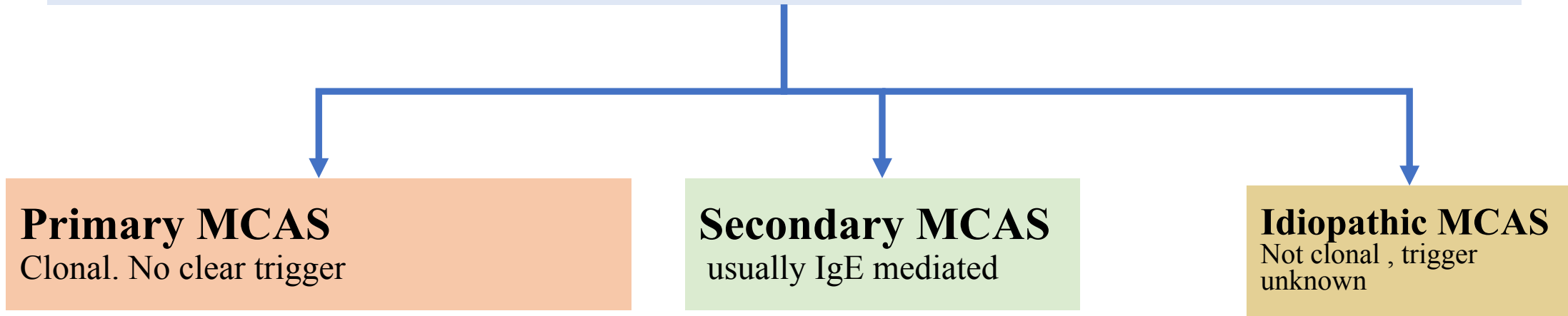
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# Hypothesis for potential link

- 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).

# Mast cell activation syndrome (MCAS)



- **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 cetrizine )**



# 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.

# Labs

- Elevated histamine metabolite ( $>230$   $\mu\text{g}$  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- $\beta$ -prostaglandin F2 alpha.

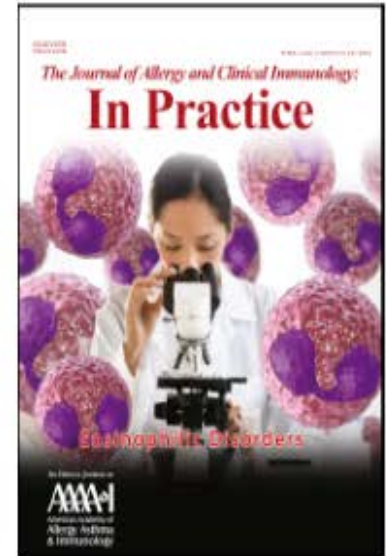
# S

- 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)

# Accepted Manuscript

Omalizumab therapy for mast cell-mediator symptoms in patients with ISM, CM, MMAS and MCAS

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**Table 1. Patients' characteristics.**

		<b>N = 55</b>
<b>General characteristics</b>		
Age at diagnosis, years, median (range)		41 (2 – 87)
Age at omalizumab treatment, years, median (range)		48 (17 – 93)
Time from diagnosis to omalizumab treatment, median (range)		3 years (2 months - 37 years)
Sex ratio (M/F)		0.44
<b>Disease classification in the whole cohort</b>		
<b>Primary MCAS (N=41)</b>	<b>Indolent Systemic Mastocytosis (ISM), N (%)</b>	29 (52.7)
	- <i>KIT</i> D816V mutation positive, N	23
	- <i>KIT</i> D816V mutation negative, N	5
	- <i>KIT</i> D816V mutation not evaluated	1
	<b>Cutaneous Mastocytosis (CM), N (%)</b>	11 (20)
	- <i>KIT</i> D816V mutation positive, N	3
	- <i>KIT</i> D816V mutation negative, N	6
	- <i>KIT</i> D816V mutation not evaluated	2
	<b>Mast Cell Activation Syndrome (MCAS), N (%)</b>	15 (27.3)
	- <i>KIT</i> D816V mutation positive (=MMAS), N	1
<b>Idiopathic MCAS (N=14)</b>	- <i>KIT</i> D816V mutation negative, N	11
	- <i>KIT</i> D816V mutation not evaluated	3

# 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.

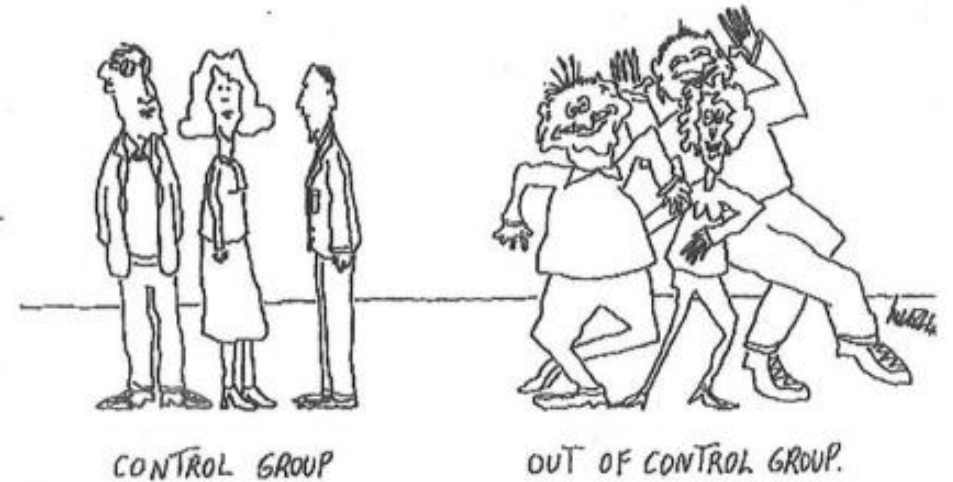
	All patients (N=55)	Primary MCAS (N=41)				Idiopathic MCAS (N=14)
		All (N=41)	ISM (N=29)	CM (N=11)	MMAS (N=1)	
Best response						
<b>ORR, N (%)</b>	<b>43 (78.2)</b>	<b>34 (82.9)</b>	<b>23 (79.3)</b>	<b>10 (90.9)</b>	<b>1 (100)</b>	<b>9 (64.3)</b>
CR, N (%)	1 (1.8)	1 (2.4)	1 (3.4)	0	0	0
MR, N (%)	30 (54.5)	22 (53.7)	16 (55.2)	5 (45.45)	1	8 (57.1)
PR, N (%)	12 (21.8)	11 (26.8)	6 (20.7)	5 (45.45)	0	1 (7.1)
No response, N (%)	12 (21.8)	7 (17.1)	6 (20.7)	1 (9.1)	0	5 (35.7)
Response at last follow up						
<b>Persistent ORR, N (%)</b>	<b>32 (58.2)</b>	<b>25 (61)</b>	<b>17 (58.6)</b>	<b>7 (63.6)</b>	<b>1 (100)</b>	<b>7 (50)</b>
CR, N (%)	1 (1.8)	1 (2.4)	1 (3.4)	0	0	0
MR, N (%)	23 (41.8)	17 (41.5)	12 (41.4)	4 (36.3)	1	6 (42.9)
PR, N (%)	8 (14.5)	7 (17.1)	4 (13.8)	3 (27.3)	0	1 (7.1)
No persistent response, N (%)	23 (41.8)	16 (39)	12 (41.4)	4 (36.3)	0	7 (50)
No response, N (%)	12 (21.8)	7 (17.1)	6 (20.7)	1 (9.1)	0	5 (35.7)
Loss of response, N (%)	4 (7.3)	3 (7.3)	2 (6.9)	1 (9.1)	0	1 (7.1)
Intolerance, N (%)	3 (5.4)	3 (7.3)	1 (3.4)	2 (18.2)	0	0
Lost from follow-up, N (%)	4 (7.3)	3 (7.3)	3 (10.3)	0	0	1 (7.1)

ORR: overall response rate, CR: complete response, MR: major response, PR: partial response



# 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.



# BN

- 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  $\mu\text{g/L}$ ) and normal at baseline (3.4  $\mu\text{g/L}$ ).
- 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 .

[Xu et al. Allergy Asthma Clin Immunol.](#) 2014 Jul 22;10(1):38. doi: 10.1186/1710-1492-10-38.

eCollection 2014.**Anaphylaxis-related deaths in Ontario: a retrospective review of cases from**

1986 to 2011

# Anaphylaxis due to an unknown trigger vs IA

**Table 3** Anaphylaxis triggers

Type of anaphylaxis trigger	BCCH (n=346)	MCH (n=631)	Diff BCCH – MCH
Food trigger (% , multinomial 95% CI)	91.3 (88.7, 94.0)	82.4 (79.7, 85.3)	8.9 (4.5, 13.3)
Among all food-triggered reactions			
PN	24.7 (20.1, 29.9)	19.0 (15.8, 22.7)	5.6 (–0.4, 11.7)
TNs	19.0 (14.9, 23.8)	16.0 (13.0, 19.5)	3.0 (–2.6, 8.6)
PN/TNs/nuts unclear	7.9 (5.3, 11.6)	6.5 (4.6, 9.1)	1.4 (–2.5, 5.3)
Milk	4.8 (2.8, 7.8)	6.7 (4.8, 9.3)	–2.0 (5.4, 1.5)
Egg	6.0 (3.8, 9.4)	7.9 (5.8, 10.6)	–1.9 (–5.6, 1.9)
Shellfish	1.9 (0.08, 4.3)	2.9 (1.7, 4.8)	–1.0 (–3.3, 1.4)
Sesame	2.2 (1.0, 4.7)	1.9 (1.0, 3.6)	0.2 (–2.0, 2.6)
Fish	2.5 (1.2, 5.1)	2.7 (1.5, 4.6)	–0.2 (–2.5, 2.2)
Kiwi	0.6 (0.1, 2.5)	0.4 (0.01, 1.5)	0.2 (–1.0, 1.5)
Soy	0	0.6 (0.1, 1.8)	–0.6 (–1.5, 0.3)
Wheat	1.9 (0.08, 4.3)	0.8 (0.2, 2.1)	1.1 (–0.8, 3.1)
Nonfood triggers			
Venom	0.9 (0.0, 3.6)	1.4 (0.0, 4.3)	–0.6 (–2.1, 1.0)
Drug	2.0 (0.0, 4.7)	3.6 (0.9, 6.5)	–1.6 (–3.9, 0.7)
Other	0.9 (0.0, 3.6)	2.1 (0.0, 5.0)	–1.2 (–2.9, 0.5)
Unknown	4.9 (2.3, 7.6)	10.5 (7.7, 13.4)	–5.5 (–9.1, 2.0)

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30 December 2016

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**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

## **Anaphylaxis to hidden pea protein: A Canadian pediatric case series**

Elana Laving, MD<sup>a,b</sup>, and Moshe Ben-Shoshan, MD<sup>c</sup>

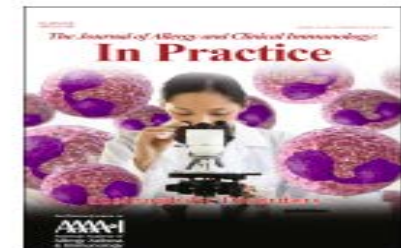
### *Clinical Implications*

- Pea-derived ingredients in food products may be a relatively underrecognized source of allergy and anaphylaxis. A pediatric case series illustrates a wide range of foods that may contain pea protein.

## Accepted Manuscript

Emergency Management of Anaphylaxis due to an Unknown Trigger: An 8-year follow-up study in Canada

Michelle Le, BSc, Sofianne Gabrielli, MSc, Ann Clarke, MD MSc FRCPC, Harley Eisman, MD, Judy Morris, MD MSc, Jocelyn Gravel, MD MSc, Edmond S. Chan, MD FAAAAI, Rod Lim, MD, Andrew O'Keefe, MD, Greg Shand, MSc, Moshe Ben-Shoshan, MD MSc



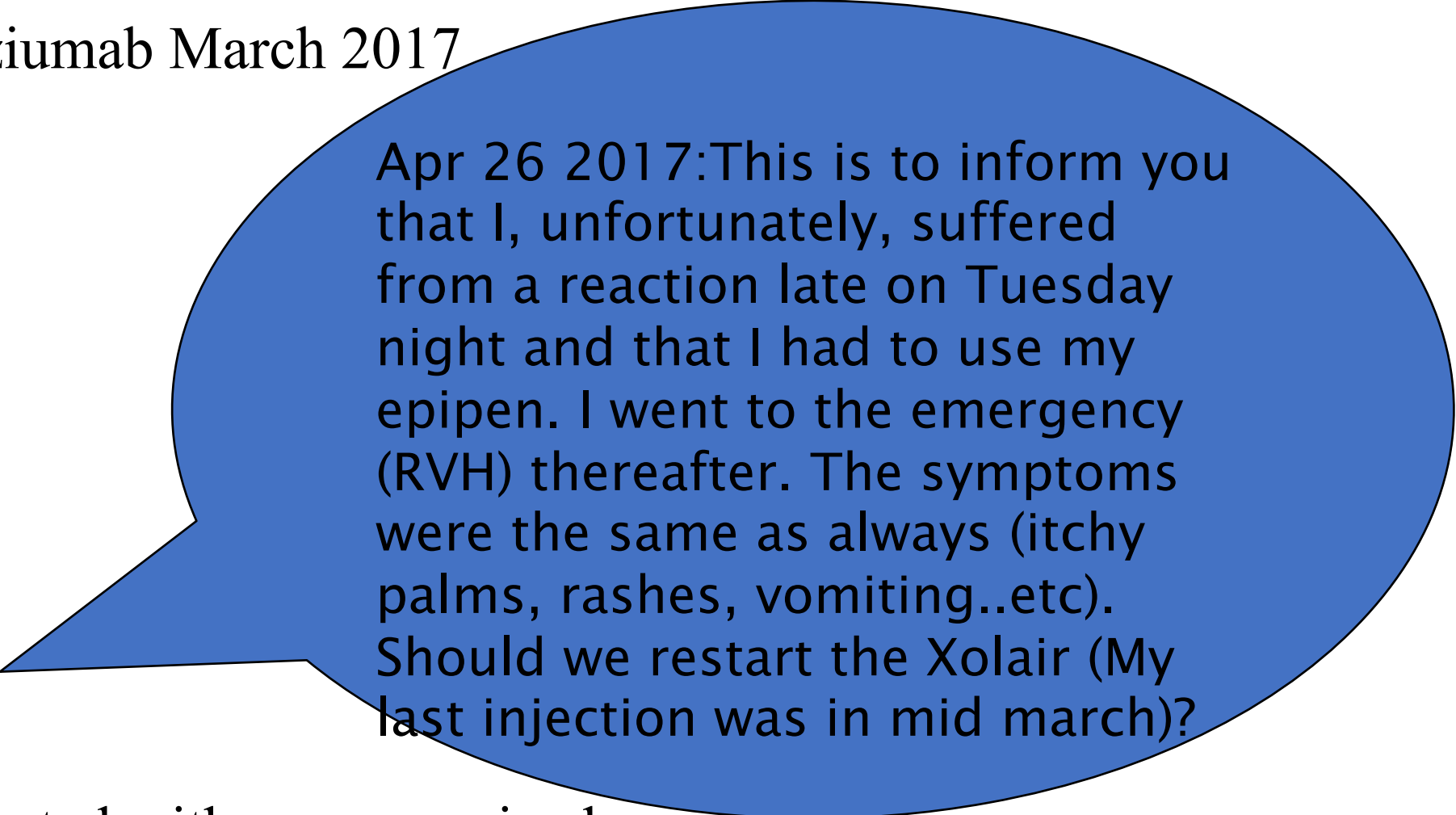
# Tx

- Frequent episodes :Continuous prednisone at a dose of 40-60 mg, antihistamine (e.g. cetirizine 10 mg) and sympathomimetics (eg 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 omalziiumab March 2017

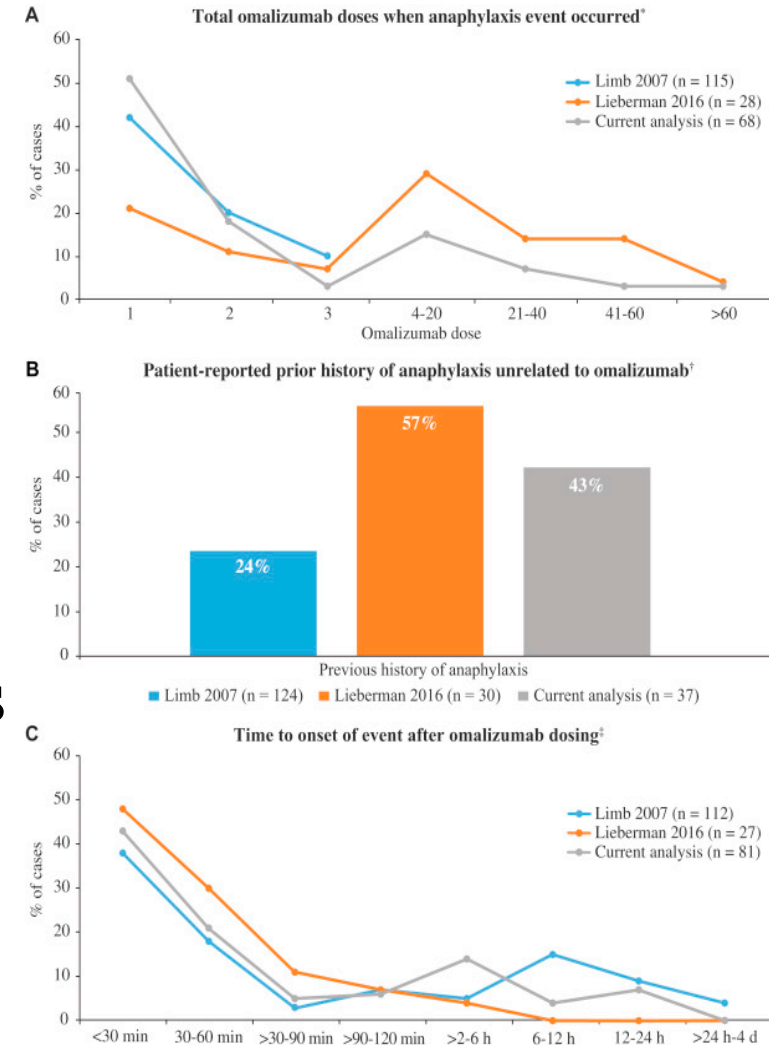


Apr 26 2017: This is to inform you that I, unfortunately, suffered from a reaction late on Tuesday night and that I had to use my epipen. I went to the emergency (RVH) thereafter. The symptoms were the same as always (itchy palms, rashes, vomiting..etc). Should we restart the Xolair (My last injection 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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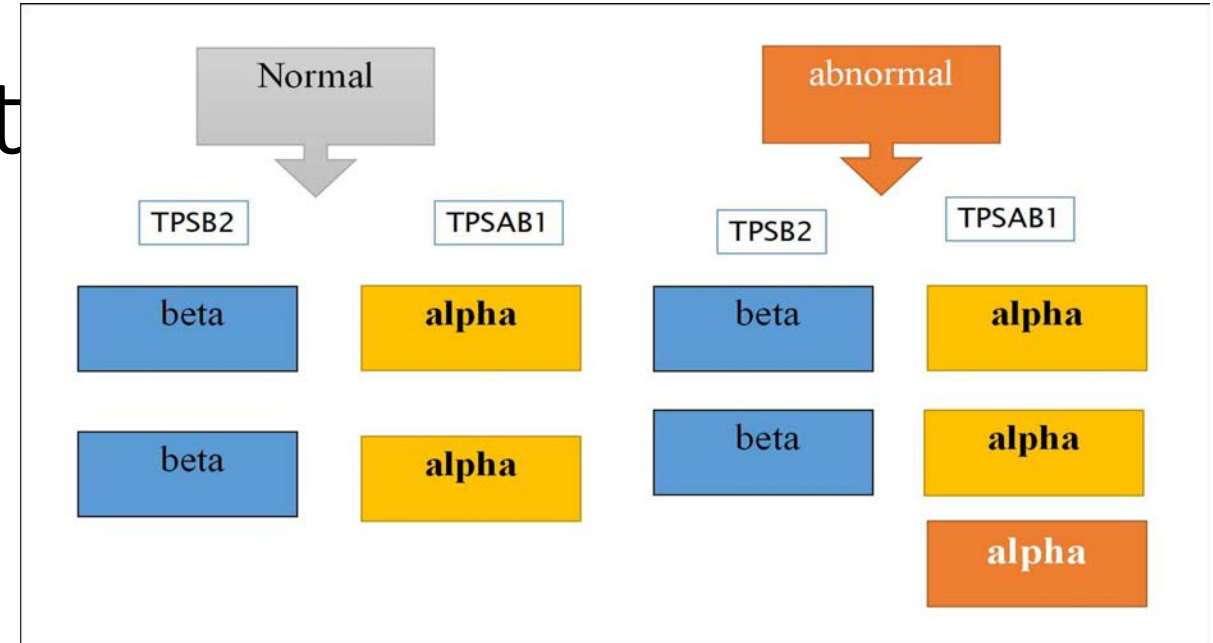
## Abstract GUF meeting . Berlin 1017

# 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 disorders are a challenging diagnosis
- High morbidity and risk of mortality
- Omalizumab is likely to benefit various pathologies in which Mast cells play a major role but large scale studies are required to establish its effect and safety .
- Future studies exploring modified omalizumab protocols for 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