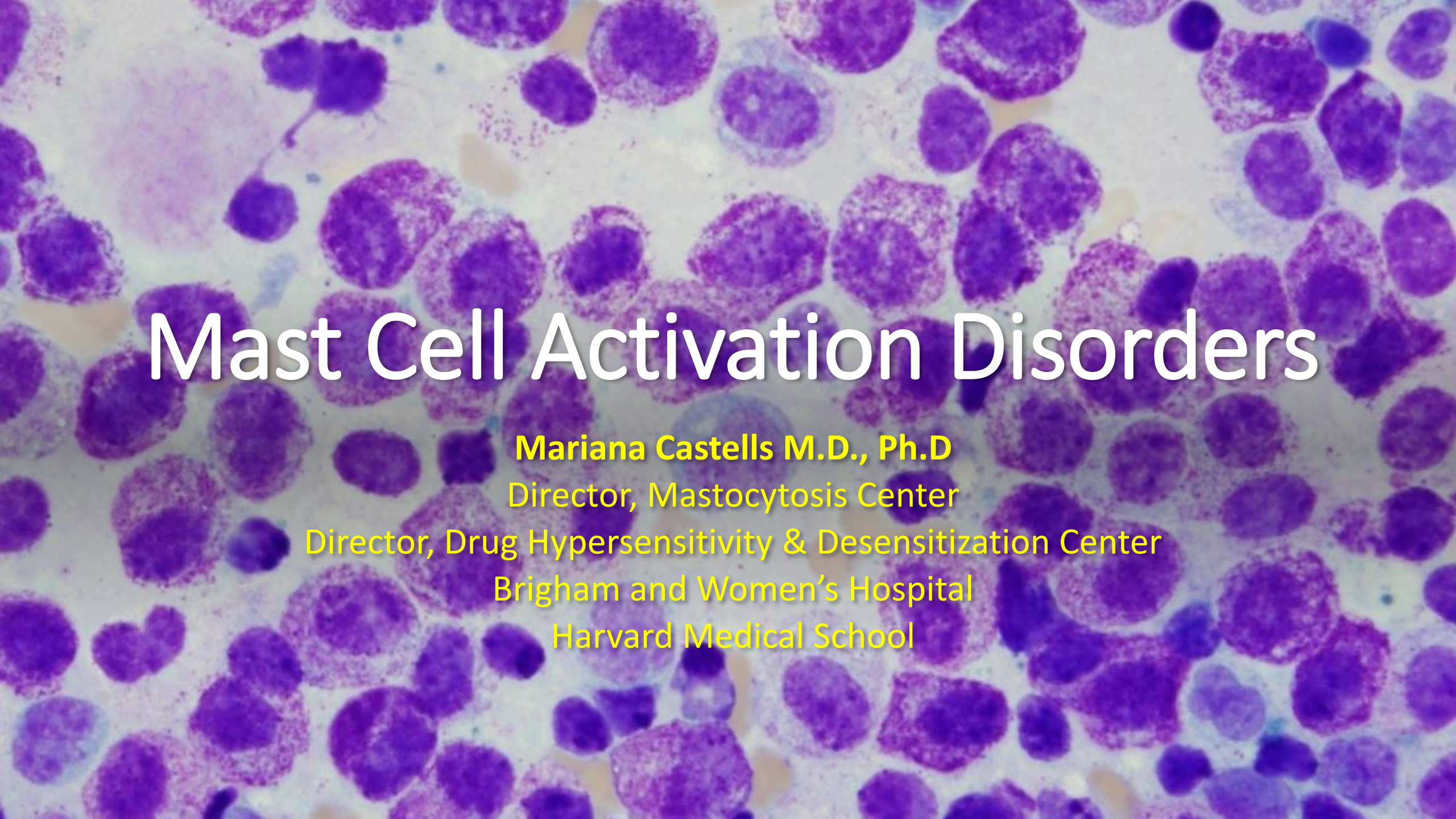


Mast Cell Activation Disorders

Mariana Castells M.D., Ph.D
Director, Mastocytosis Center
Director, Drug Hypersensitivity & Desensitization Center
Brigham and Women's Hospital
Harvard Medical School

Learning Objectives

1. To understand the scope of mast cell activation disorders
2. To address the presentations of mast cell activation disorders with their associated endotypes
3. To evaluate the role of *KIT* D816V mutation and *TPSAB1* genotyping in the diagnosis of mast cell activation disorders
4. To review current and future management and treatment options for mast cell activation disorders

The Journal of Allergy and Clinical Immunology: In Practice
Volume 9, Issue 5, May 2021, Pages 2083-2086

Clinical Communications

COVID-19 infection in patients with mast cell disorders including mastocytosis does not impact mast cell activation symptoms

Matthew P. Giannetti MD [a, b], Emily Weller BA [a], Iván Alvarez-Twose MD, PhD [c], Inés Torrado MD [c], Patrizia Bonadonna MD [d], Roberta Zanotti MD [e], Daniel F. Dwyer PhD [a, b], Dinah Foer MD [a, b], Cem Akin MD, PhD [f], Karin Hartmann MD [g], Tiago Azenha Rama DMD, MD [h, i], Wolfgang R. Sperr MD [j], Peter Valent MD [j], Cristina Teodosio PhD [k], Alberto Orfao MD, PhD [l], Mariana Castells MD, PhD [a, b]

28 patients:

- 24 clonal mast cell disorders
- 4 elevated tryptase MCAS/Hereditary Alpha Tryptasemia
- 14F, 12M
- Ages 6-77
- 100% of patients had no mast cell activation symptoms or anaphylaxis

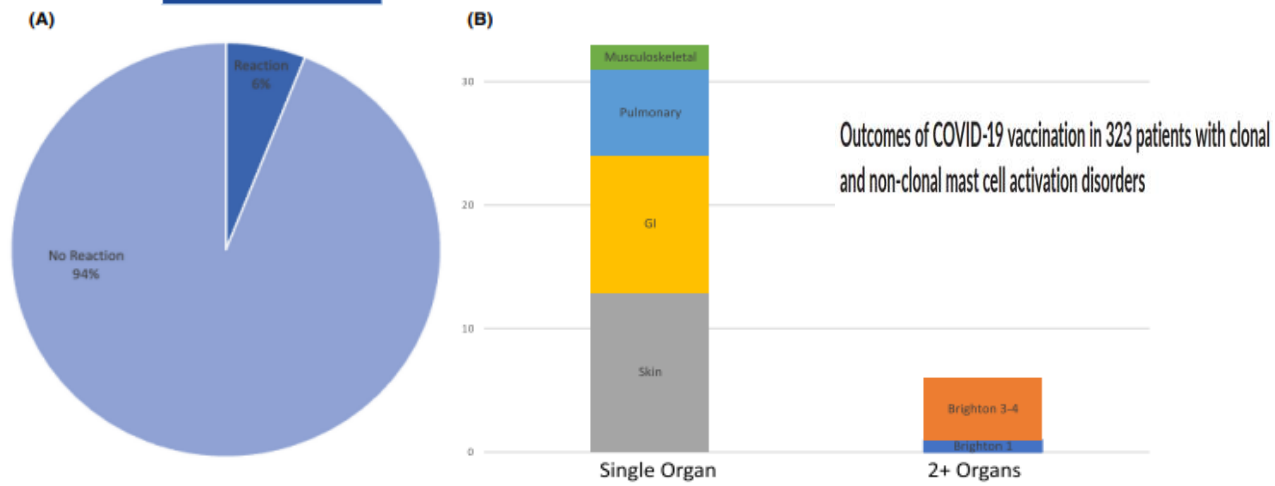
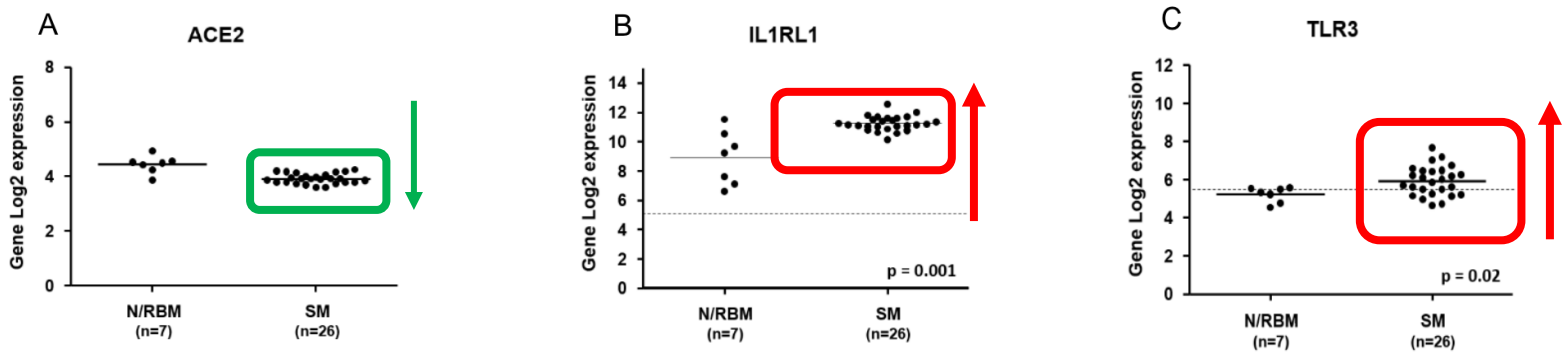
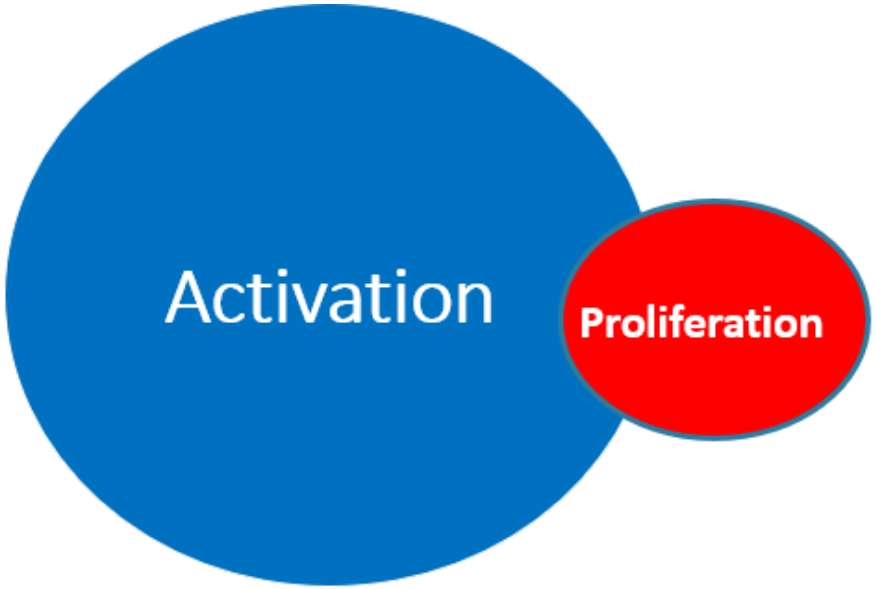


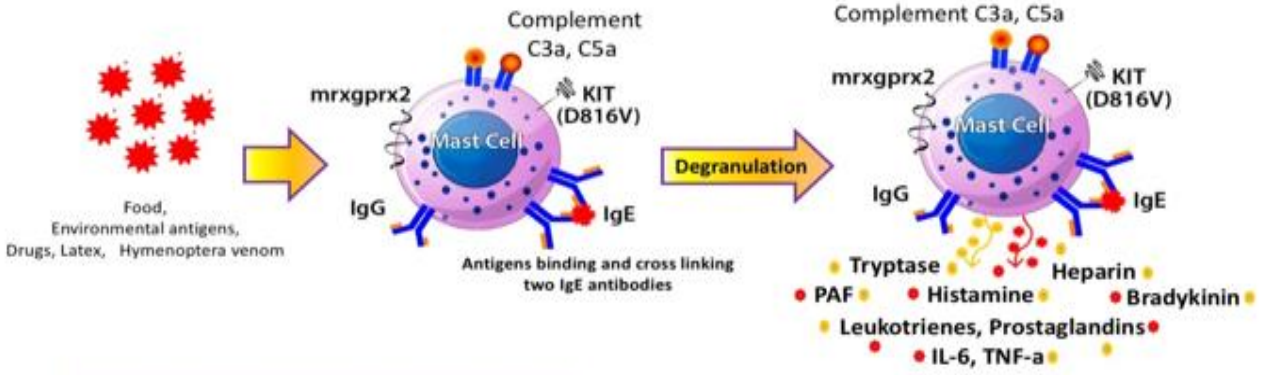
FIGURE 1 Characterization of adverse reactions to COVID-19 vaccination. (A) graphical depiction of percentage of patients with adverse reaction or no reaction. (B) Brighton Criteria scoring in adverse reactions to COVID-19 vaccination involving two or more organ systems.



Gene expression of ACE2, TLR3, and IL1RL1 on highly purified bone marrow mast cells normal/reactive N/RBM (n=7) and systemic mastocytosis SM patients (n=26)

Selecting the Right Criteria and Proper Classification to Diagnose Mast Cell Activation Syndromes: A Critical Review 2022



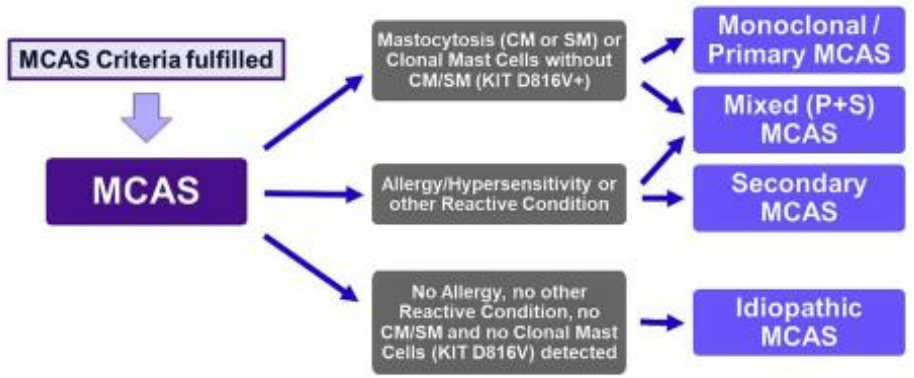


Position Paper

International Archives of Allergy and Immunology
Int Arch Allergy Immunol 2012;157:215–225
DOI: 10.1159/000328760
Received: January 24, 2011
Accepted after revision: April 18, 2011
Published online: October 27, 2011

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

Classification of MCAS



Mast Cell Activation Syndrome (MCAS)

Diagnostic criteria

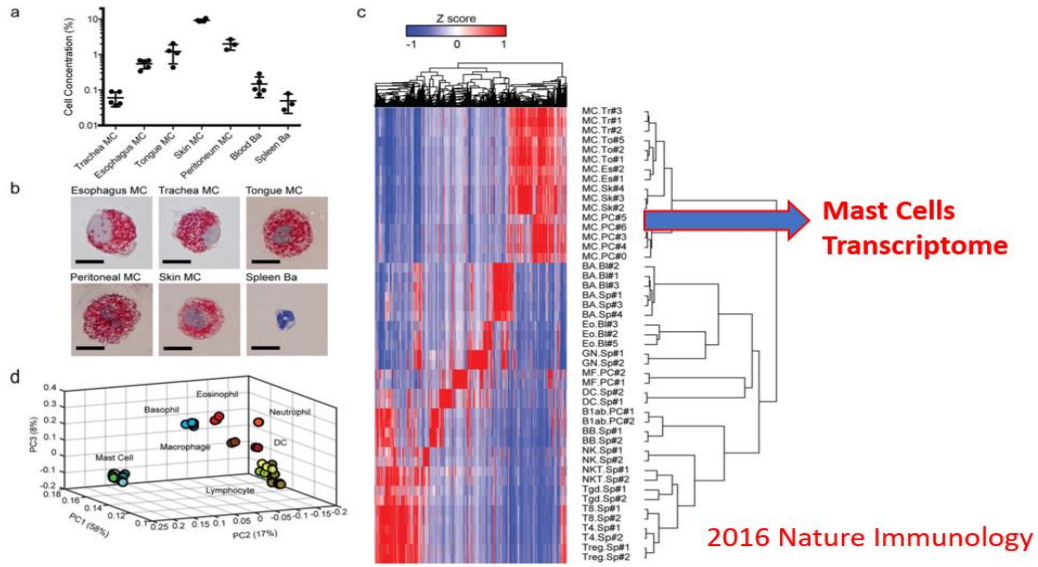
- 1. Episodic multisystem symptoms consistent with mast cell activation
- 2. Appropriate response to medications targeting mast cell activation
- 3. Documented increase in validated markers of mast cell activation systemically during a symptomatic period

Symptoms (two or more organs):

- **SKIN**: Itching, Rash, Flushing, Hives.
- **Gastro-Intestinal (GI)**: Abdominal pain, Diarrhea, Bloating, Nausea.
- **Respiratory**: Closing Throat, Chest Tightness, Wheezing, Shortness of breath.
- **Central Nervous System**: Brain Fog, Short Memory Span or Inability to Concentrate.
- **Cardiovascular**: Dizziness, Presyncope or Syncope
- **Bone**: Pain, Osteopenia, Osteoporosis, Fractures.
- **Others**: Joints and muscles pain, Fatigue.
- **Anaphylaxis.**

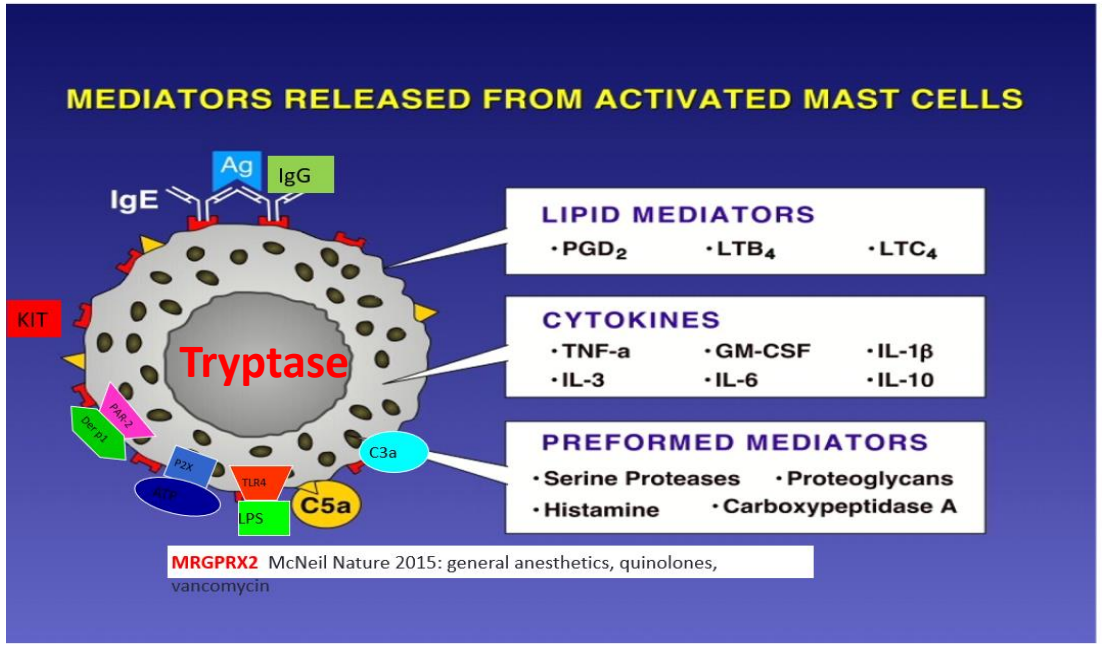
Expression profiling of constitutive mast cells reveals a unique identity within the immune system

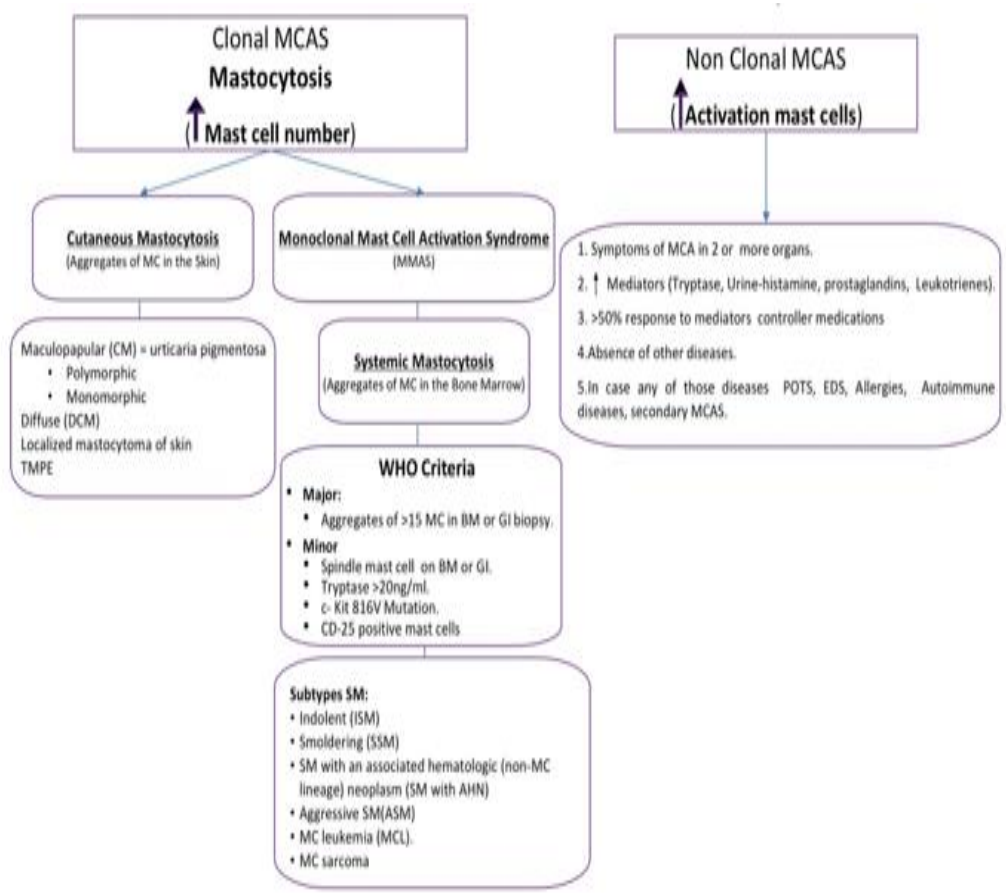
Daniel F. Dwyer[1,2], Nora A. Barrett[1,2,*], K. Frank Austen[1,2,*], and The Immunological Genome Project Consortium[3]



Mast Cells Transcriptome

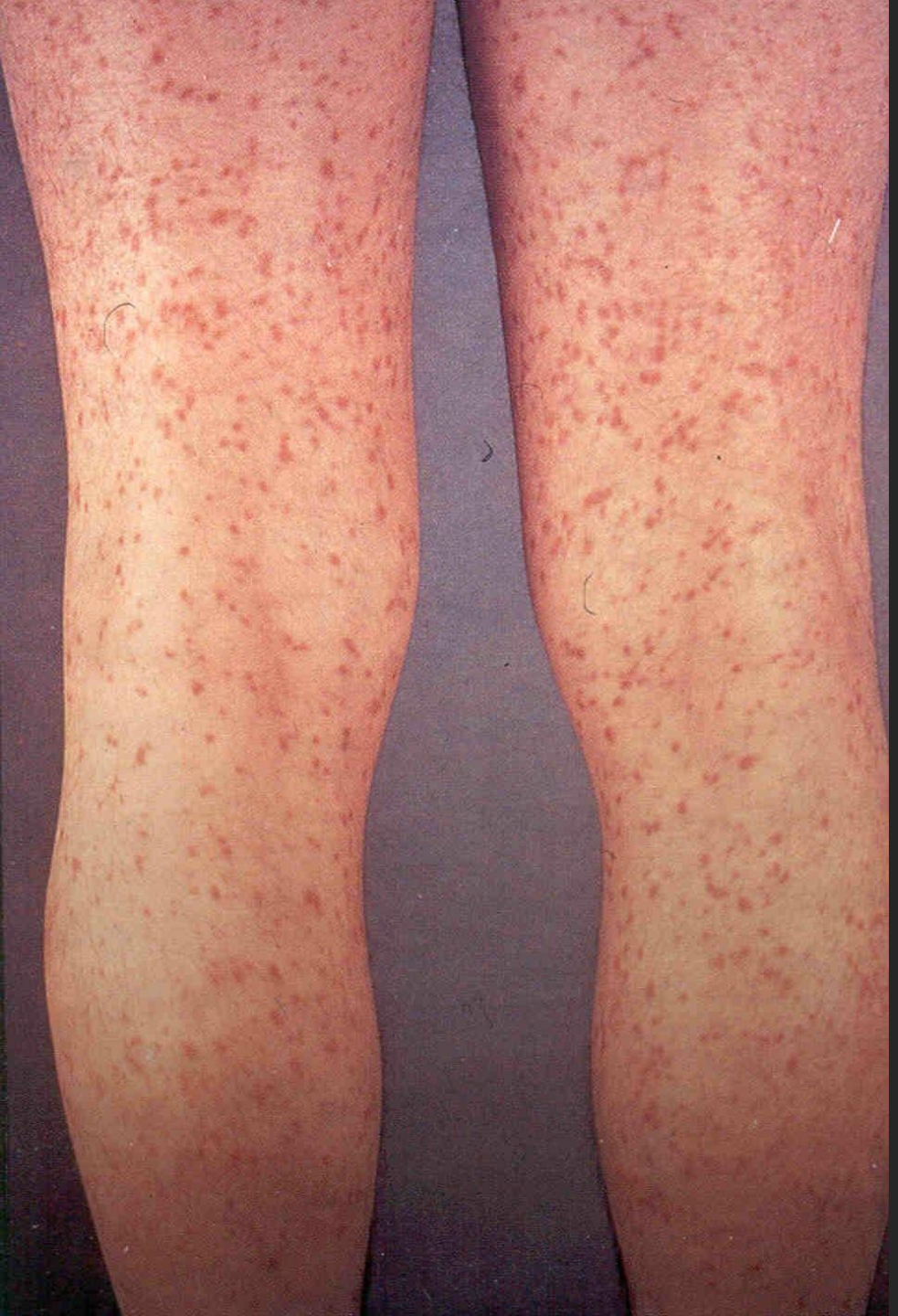
2016 Nature Immunology





Clonal Mast Cell Activation Disorders

- Increased number of mast cells
- *KIT* mutations: most common D816V
- Symptoms and signs of mast cells tissues increase and/or activation
  - Skin: cutaneous mastocytosis (brown/red lesions)
  - Bone Marrow: mast cell aggregates, expression of CD25
  - Gastrointestinal: increased mast cells in aggregates, CD25 +



The New York Times Magazine

“Mommy, I am scared. Are you OK?”

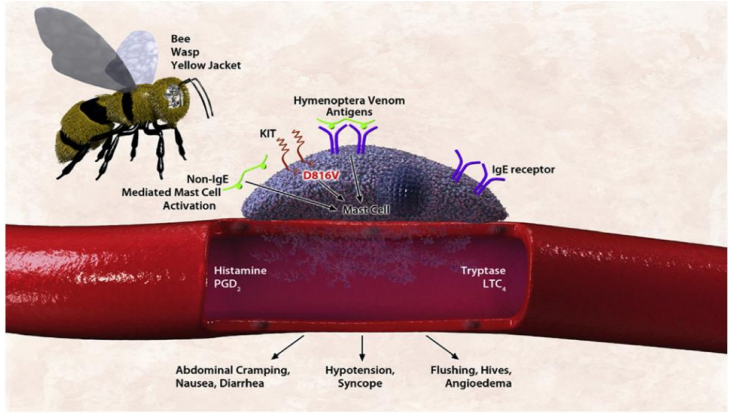
A 32 y/o mother was lying unconscious in a public bathroom after feeling, hot, dizzy and a fluttering heart.

She told the ER doctors that her only medical problems were **panic attacks, flushing and a rash** that she had for over 10 years and was told it was freckles

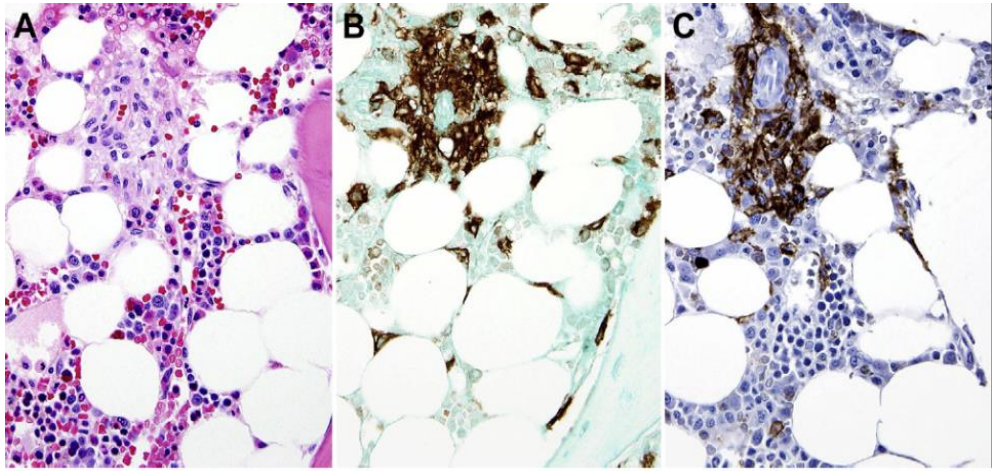
Anaphylaxis After Hymenoptera Sting: Is It Venom Allergy, a Clonal Disorder, or Both?

Mariana C. Castells, MD, PhD, Jason L. Hornick, MD, PhD, and Cem Akin, MD, PhD *Boston, Mass*

A 47-year-old man presented with loss of consciousness 5 minutes after being stung by a yellow jacket in his backyard. Epinephrine and fluids were required for resuscitation. Allergy evaluation revealed specific IgE to yellow jacket and honeybee, and the patient was started on venom immunotherapy. He had systemic reactions during buildup and a severe anaphylactic episode requiring 3 doses of intramuscular epinephrine at maintenance doses. Immunotherapy was discontinued. Serum tryptase level after 1 such episode was 29 ng/mL, with a baseline level of 25 ng/mL 4 weeks later. The physical examination was unremarkable including no skin lesions of cutaneous mastocytosis. Because of elevated baseline tryptase level, a bone marrow biopsy was performed, which revealed multifocal dense infiltrates of mast cells. A diagnosis of systemic mastocytosis was made. The patient was treated with omalizumab and was able to tolerate immunotherapy and is currently maintained on lifelong immunotherapy. He was restung in the field and has not had anaphylaxis. (J Allergy Clin Immunol Pract 2015;3:350-5)



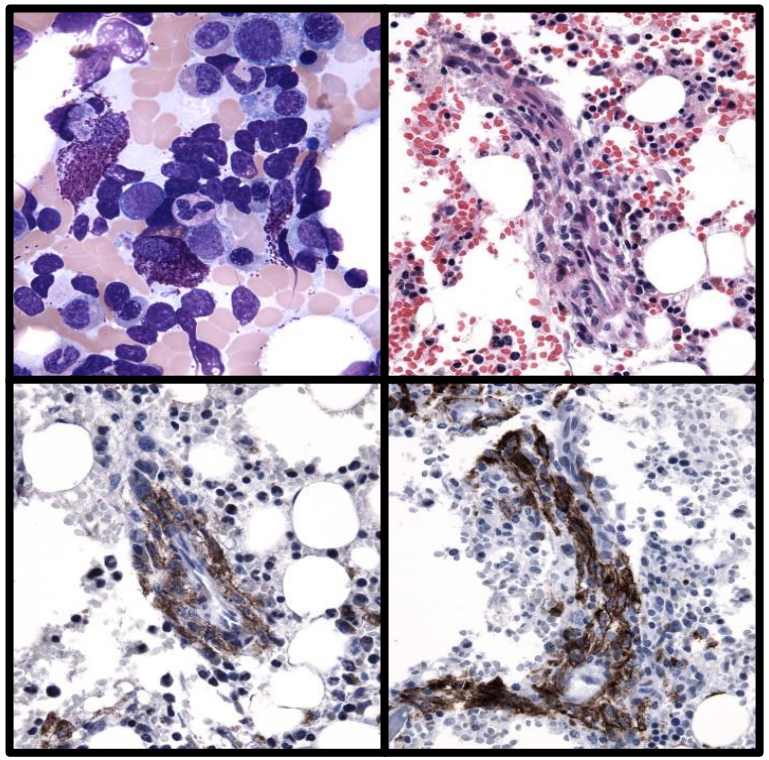
Tryptase KIT



- 33 y/o male runner Boston Marathon
- Joint pain 800 mg Ibuprofen
- Flushing, hypotension, SOB, intubation
- **Tryptase of >2000 ng/ml**

- Symptoms: flushing, chronic fatigue, depression, anxiety, bone pain, chest pain (multiple MI r/o)
- PE: **few macular lesions in chest** (CM)
- BMB: **MC aggregates, CD25 +**
- Positive c-kit D816V mutation
- **Baseline tryptase: 32 ng/ml**

Systemic Mastocytosis

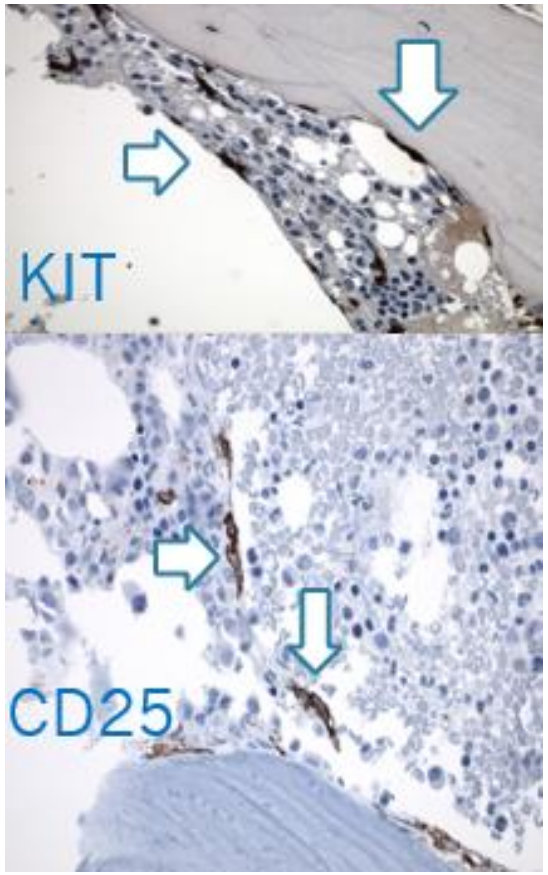


Mandakolathur Murali, M.D.
Mariana C. Castells, M.D., Ph.D.
David M. Dudzinski, M.D., J.D.
James Song, M.D.
Robert P. Hasserjian, M.D.
NEJM 2011

Anaphylaxis During Immunotherapy

- 44 y/o female with seasonal rhinitis ST + grasses, ragweed
- Immunotherapy: burning hands and feet, chest pressure, lightheadedness **Epinephrine**
- Severe cramping, abdominal pain, nausea, vomiting, dizziness, feet and hand burning and feeling of impending doom, no hives
- ER: 60/30 **multiple Epinephrine**

- **Tryptase: 8.75 ng/ml total, <1 ng/ml mature**
- **PB : c-kit D816V mutation +**
- **IgE : 18 IU/ml; Specific IgE foods (-)**
- **BMB: no MC aggregates, spindle MC,Positive CD25 MC**

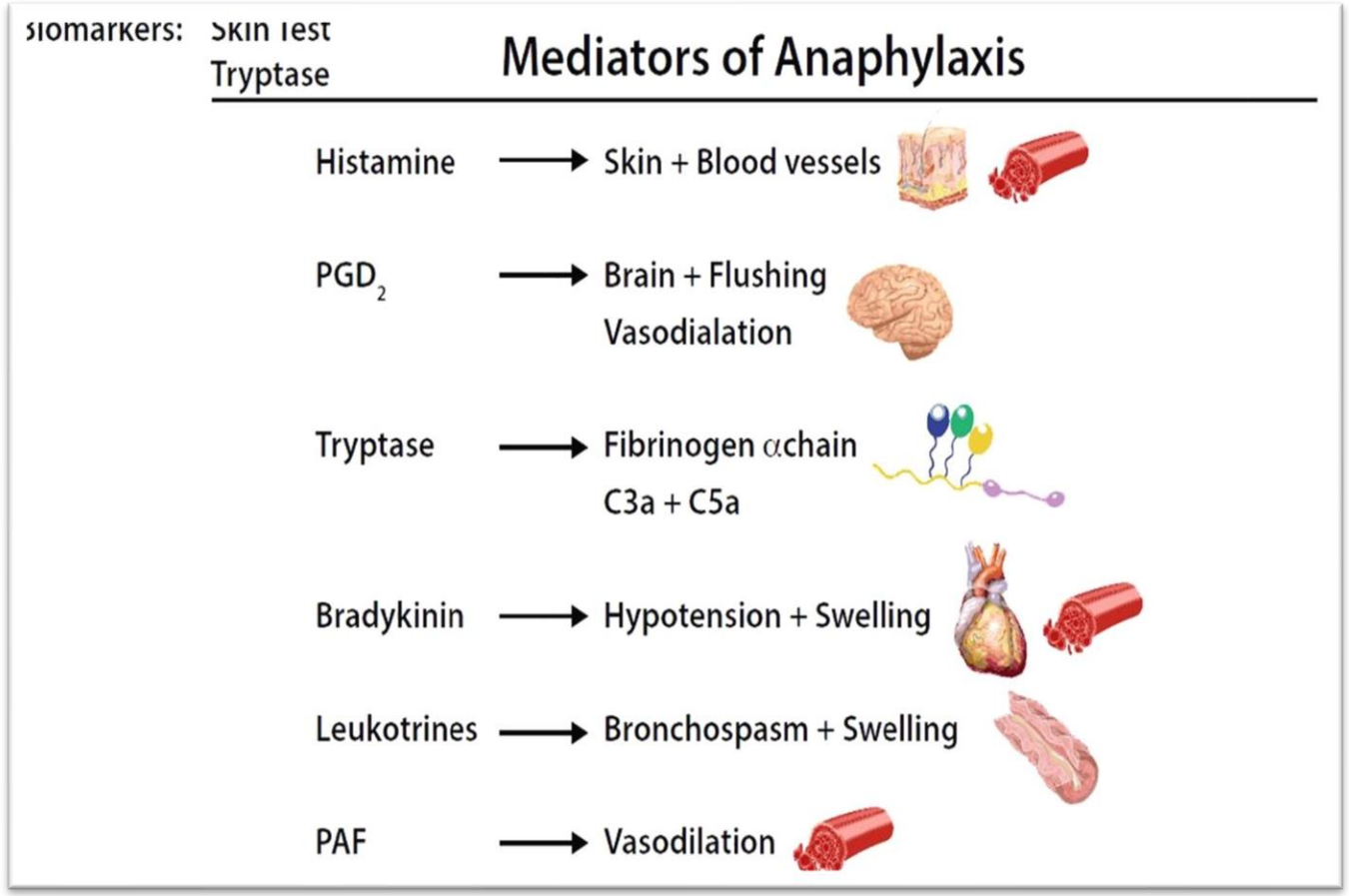


Monoclonal Mast Cell Activation Syndrome

Mast Cell Mediators and Related Symptoms

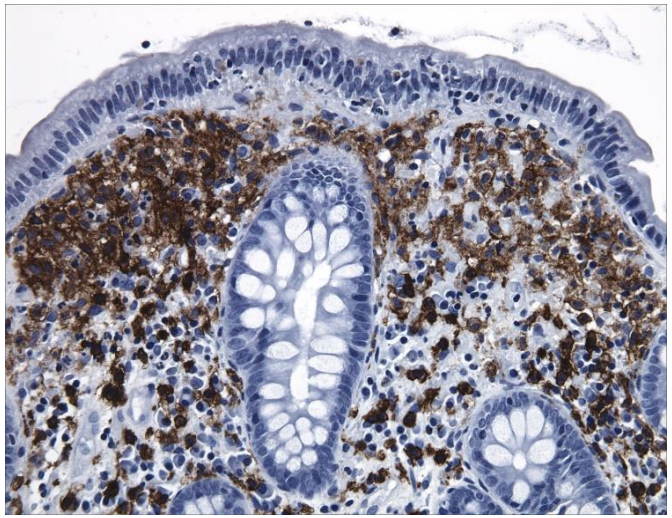
Table 1 Mast cell mediators and related symptoms

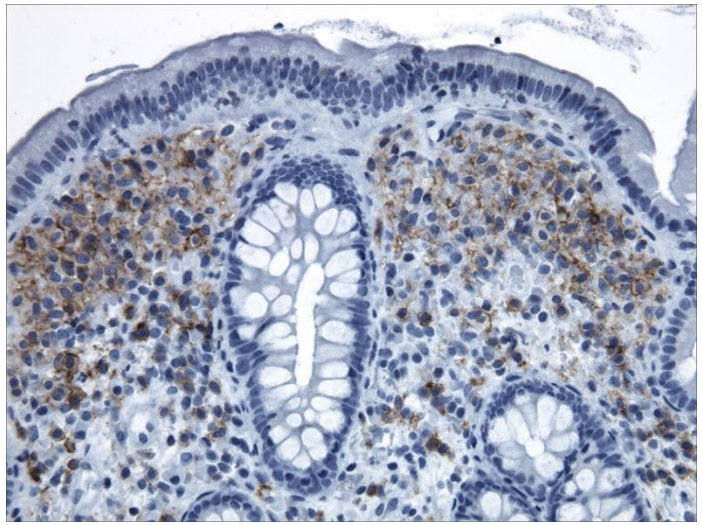
	Mediator(s)	Measured in mastocytosis
Systemic		
Vasodilation/hypotension	Histamine	+
	Prostaglandin D2	+
Hypertension	Chymase	–
Fatigue/cachexia/weight loss	TNF-α	+
Fever	IL-6	+
	IL-1	–
Fibrosis	IL-1	–
	IL-13	–
	TGF-β	–
Skin		
Flushing	Histamine	+
	Prostaglandin D2	+
Urticaria/angioedema	Histamine	+
	Prostaglandin D2	+
	Leukotriene C4	–
Gastrointestinal		
Abdominal pain	Histamine	+
Peptic		
Colic		
Diarrhea	Histamine	+
Malabsorption		
Bone		
Bone pain		
Osteoporosis/osteopenia	IL-6	+
	Heparin	–
	Tryptase	+
	TGF-β	–
Central nervous system		
Mixed CNS syndrome	Prostaglandin D2	+
	Histamine	+



Mast Cells Gastrointestinal Infiltration in Systemic Mastocytosis

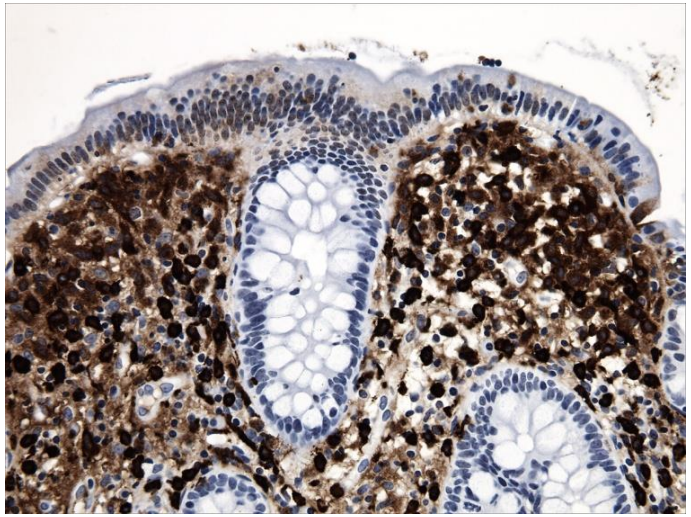
KIT





Tryptase

CD25



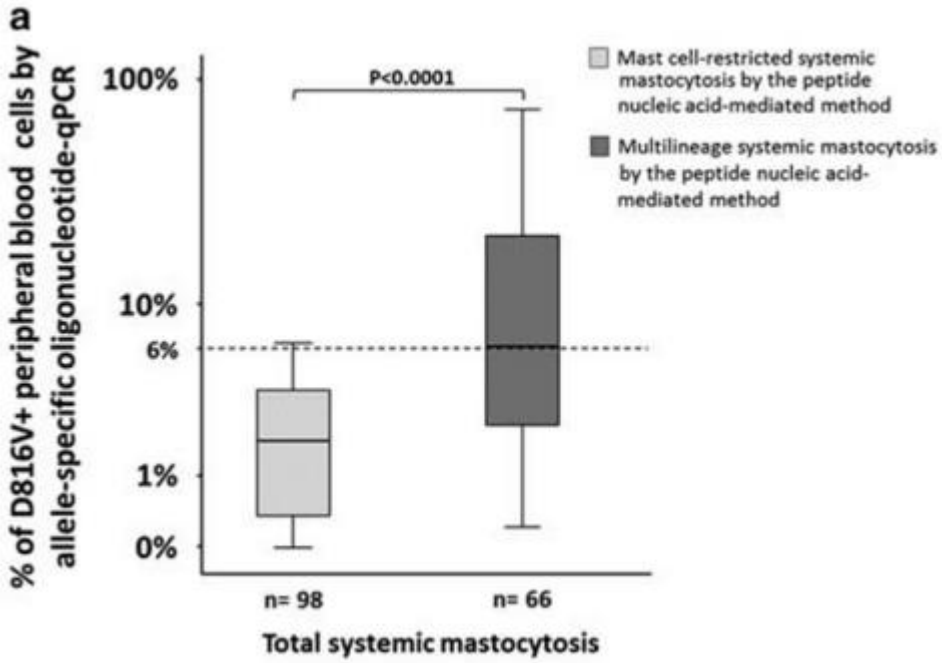
A Clinicopathologic Study of 24 Cases of Systemic Mastocytosis Involving the Gastrointestinal Tract and Assessment of Mucosal Mast Cell Density in Irritable Bowel Syndrome and Asymptomatic Patients

Leona A. Doyle, MD*, Golrokh J. Sepehr, MD*, Matthew J. Hamilton, MD†,‡, Cem Akin, MD,
PhD†,‡, Mariana C. Castells, MD†,‡, and **Jason L. Hornick, MD ,PhD 2014**

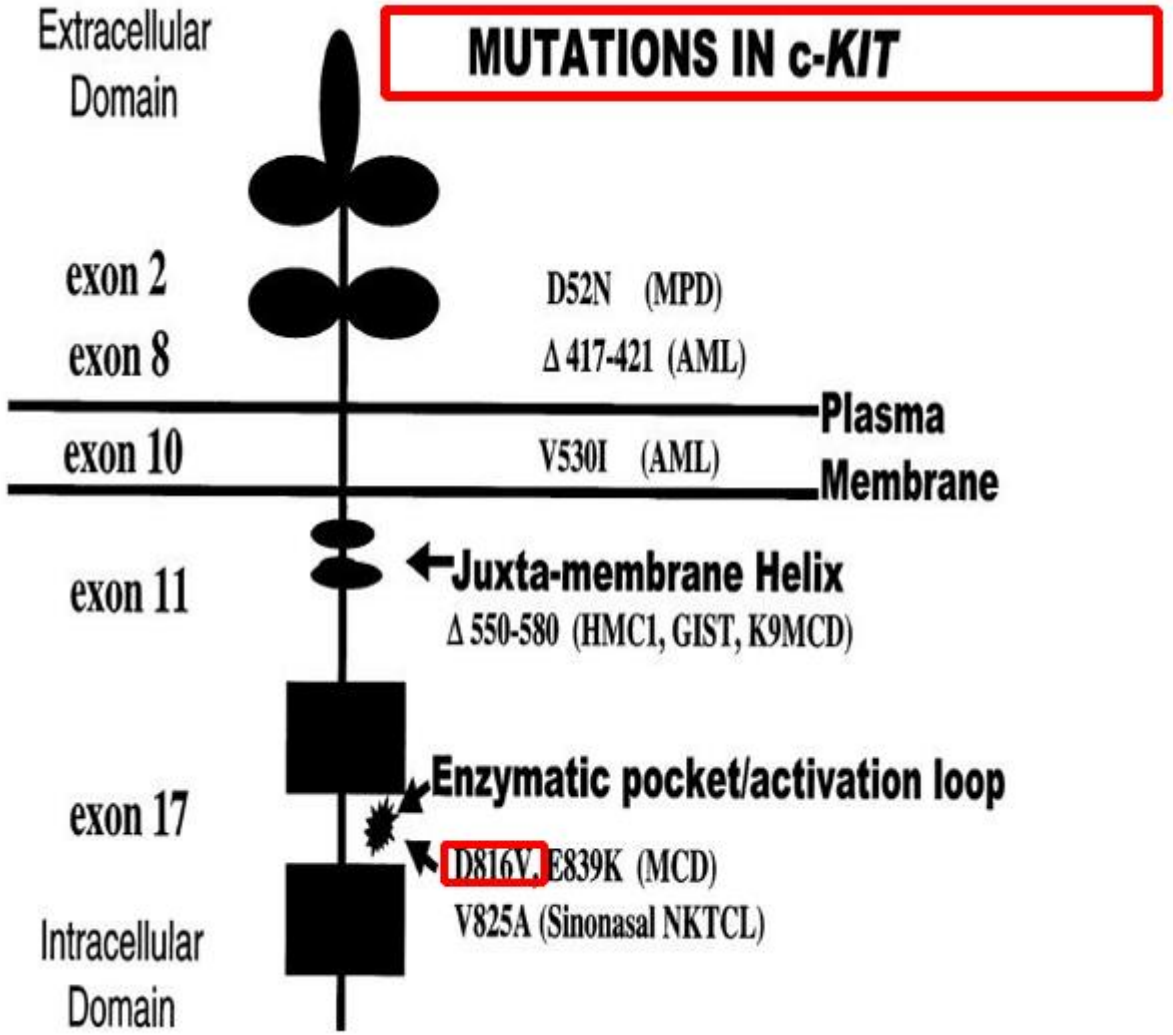
Modern Pathology (2015) 28, 1138–1149

Detection of the *KIT* D816V mutation in peripheral blood of systemic mastocytosis: diagnostic implications

Maria Jara-Acevedo[1], Cristina Teodosio[2], Laura Sanchez-Muñoz[3], Ivan Álvarez-Twose[3], Andrea Mayado[1], Carolina Caldas[1], Almudena Matito[3], José M Morgado[3], Javier I Muñoz-González[1], Luis Escribano[1], Andrés C Garcia-Montero[1,4] and Alberto Orfao[1,4]



10% of Mastocytosis are negative for KITD816V



From: Longley, B.J. *et. al., Leukemia Research 25:* 571-576, 2001.

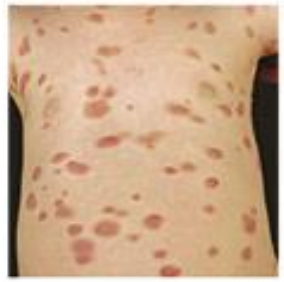
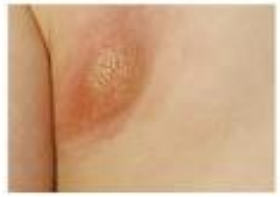
Task force report

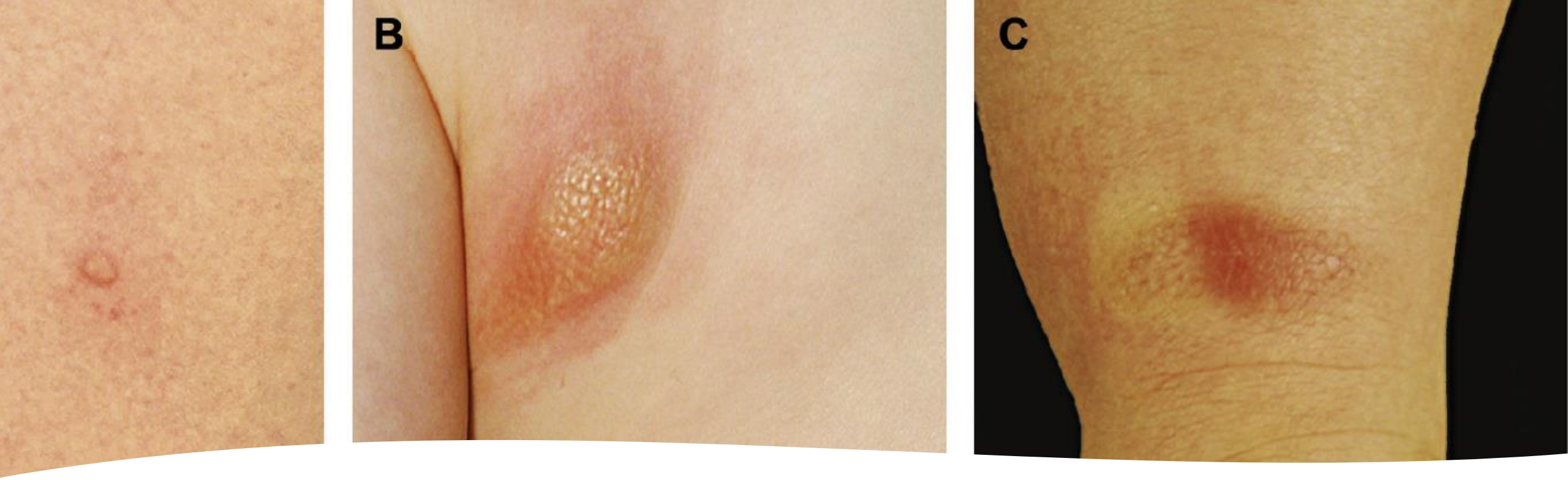
Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology

JACI 2016

Karin Hartmann, MD,[a,b] Luis Escribano, MD, PhD,[c] Clive Grattan, MA, MD,[d] Knut Brockow, MD,[e] Melody C. Carter, MD,[f] Ivan Alvarez-Twose, MD,[g] Almudena Matito, MD, PhD,[g] Sigurd Broesby-Olsen, MD,[h] Frank Siebenhaar, MD,[i] Magdalena Lange, MD, PhD,[j] Marek Niedoszytko, MD, PhD,[k] Mariana Castells, MD, PhD,[l] Joanna N. G. Oude Elberink, MD, PhD,[m] Patrizia Bonadonna, MD,[n] Roberta Zanotti, MD,[o] Jason L. Hornick, MD, PhD,[p] Antonio Torrelo, MD,[q] Jürgen Grabbe, MD,[r] Anja Rabenhorst, PhD,[a] Boguslaw Nedoszytko, PhD,[j] Joseph H. Butterfield, MD,[s] Jason Gotlib, MD,[t] Andreas Reiter, MD,[u] Deepti Radia, MD,[v] Olivier Hermine, MD, PhD,[w] Karl Sotlar, MD,[x] Tracy I. George, MD,[y] Thomas K. Kristensen, PhD,[z] Hanneke C. Kluin-Nelemans, MD, PhD,[aa] Selim Yavuz, MD,[bb] Hans Hägglund, MD, PhD,[cc] Wolfgang R. Sperr, MD,[dd] Lawrence B. Schwartz, MD, PhD,[ee] Massimo Triggiani, MD, PhD,[ff] Marcus Maurer, MD,[i] Gunnar Nilsson, PhD,[gg] Hans-Peter Horny, MD,[x] Michel Arock, PharmD, PhD,[hh] Alberto Orfao, MD, PhD,[c] Dean D. Metcalfe, MD,[f] Cem Akin, MD, PhD,[i] and Peter Valent, MD[dd]

Cologne, Luebeck, Munich, Mannheim, and Berlin, Germany, Salamanca, Toledo, and Madrid, Spain, Norwich and London, United Kingdom, Bethesda, Md, Odense, Denmark, Gdansk, Poland, Boston, Mass, Groningen, The Netherlands, Verona and Salerno, Italy, Aarau, Switzerland, Rochester, Minn, Stanford, Calif, Paris and Cachan, France, Albuquerque, NM, Istanbul, Turkey, Stockholm, Sweden, Vienna, Austria, and Richmond, Va

Subforms	Variants	Typical manifestations
Maculopapular cutaneous mastocytosis (syn. urticaria pigmentosa)	Monomorphic	
	Polymorphic	
Diffuse cutaneous mastocytosis		
Cutaneous mastocytoma		

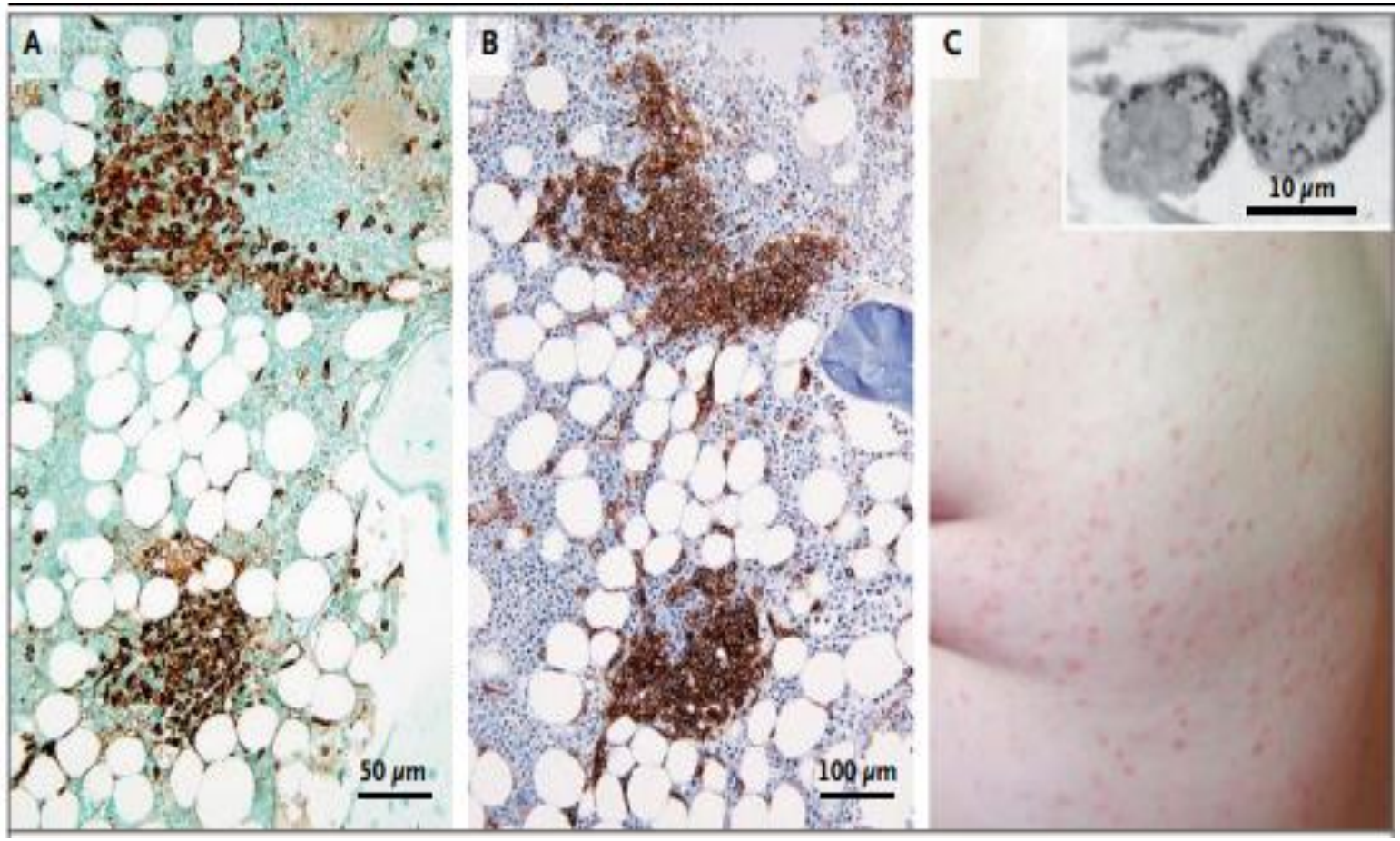


Darier’s Sign

- FIG 3. Darier’s sign. A-C, A wheal-and-flare reaction develops upon stroking of a CM lesion with a tongue spatula. Darier’s sign is a highly specific diagnostic feature of CM.

BONE MARROW BIOPSY

Urticaria Pigmentosa Skin Biopsy



Tryptase **CD25**

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Mast Cells, Mastocytosis, and Related Disorders

Theoharis C. Theoharides, Ph.D., M.D., Peter Valent, M.D., and Cem Akin, M.D., Ph.D.

Cutaneous Manifestations in Patients with Mastocytosis:

TABLE I. Characteristics of typical adulthood-onset and typical childhood-onset mastocytosis

Parameter	Adulthood-onset mastocytosis	Childhood-onset mastocytosis
Most frequent category of mastocytosis	ISM	Cutaneous mastocytosis
Typical course of the disease	Chronic	Temporary
Frequency of anaphylaxis (%)	50	<10
Typical tryptase level (μg/L)	>20	<20
Typical location of *KIT* mutation	Exon 17, most frequently *KIT* D816V	Exon 8, 9, 11, or 17 or absent
Most frequent type of cutaneous lesions	Maculopapular	Maculopapular
Typical morphology of maculopapular lesions	Monomorphic	Polymorphic
Typical size of maculopapular lesions	Small	Large
Typical distribution of maculopapular lesions	Thigh, trunk	Trunk, head, extremities

Consensus report European Competence Network on Mastocytosis
American Academy of Asthma Allergy and Immunology
European Academy of Allergology and Clinical Immunology 2016

TABLE I. Classification of mastocytosis[4]

Cutaneous mastocytosis
Systemic mastocytosis
ISM
Systemic mastocytosis associated with a hematologic disorder
Aggressive systemic mastocytosis
Mast cell leukemia
Mast cell sarcoma
Extracutaneous mastocytosis

TABLE II. Diagnostic criteria of systemic mastocytosis[4]: The major and at least 1 minor, or 3 minor criteria are needed

Major
Multifocal mast cell aggregates (>15 mast cells per aggregate) in an extracutaneous tissue (often bone marrow) biopsy
Minor
Abnormal mast cell morphology (spindle-shaped, hypogranulated)
Aberrant CD2 or CD25 expression by mast cells
Codon 816 KIT mutation in blood or lesional tissue
Baseline tryptase level >20 ng/mL (not valid in patients with other hematologic disorders)

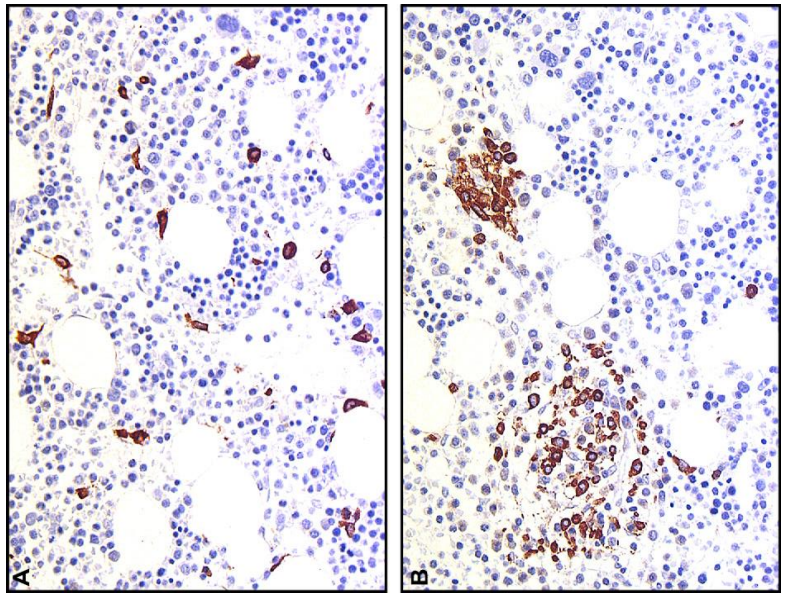
Primary Clonal Mast Cell Diseases

Well differentiated mastocytosis (WDSM)

(Alvarez Towse et al 2016)

Systemic Mastocytosis without cutaneous involvement and with hymenoptera anaphylaxis

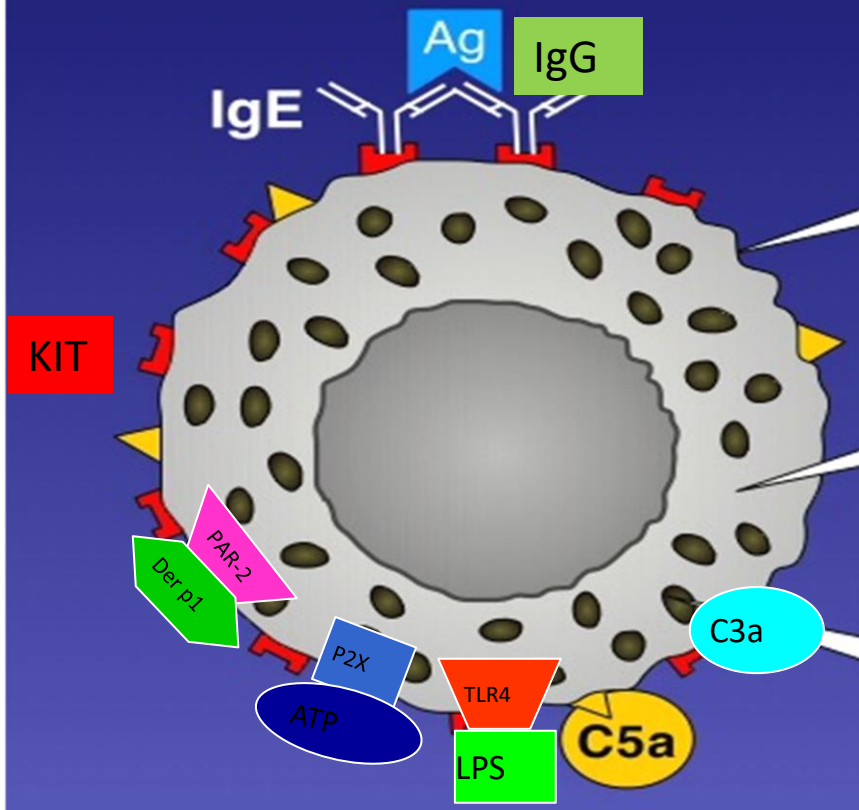
(Bonnadona et al 2016)



Monoclonal Mast Cell Activation Syndrome

Systemic Mastocytosis

MEDIATORS RELEASED FROM ACTIVATED MAST CELLS



LIPID MEDIATORS

- PGD_2
- LTB_4
- LTC_4

CYTOKINES

- TNF-a
- GM-CSF
- IL-1β
- IL-3
- IL-6
- IL-10

PREFORMED MEDIATORS

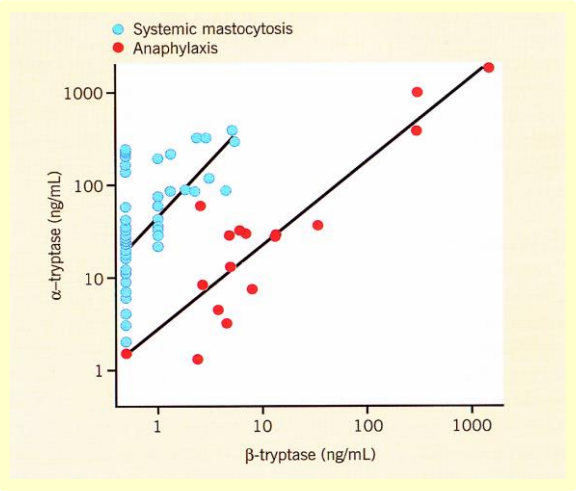
- Serine Proteases
- Proteoglycans
- Histamine
- Carboxypeptidase A

MRGPRX2 McNeil Nature 2015: general anesthetics, quinolones, vancomycin

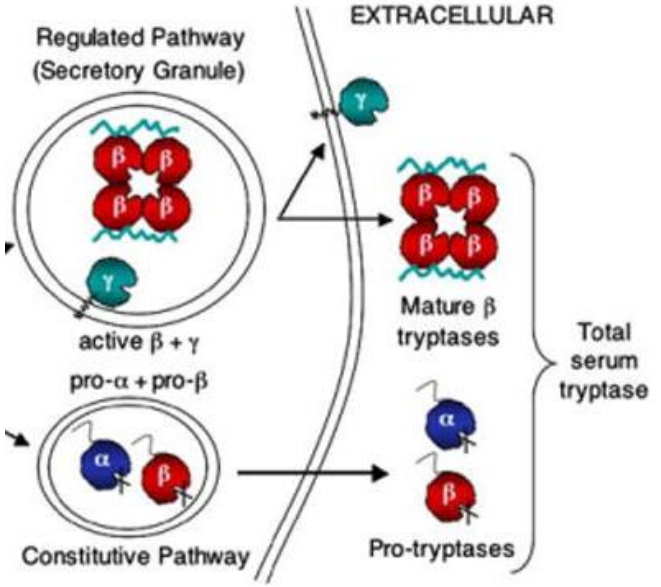
Systemic Mastocytosis: Tryptases

- **Total tryptase**
  - Mostly inactive pro-tryptase at baseline
  - Reflect mast cell burden at baseline
- **Mature β-tryptase**
  - Measure of MC activation
- **Total: mature tryptase ratio**
  - >20 in SM at baseline
  - <10 during systemic anaphylaxis
- **27 % Caucasian lack an alpha tryptase gene**
- **Low baseline tryptase**
  - (Significant elevation: > 20% baseline+ 2 ng)

Normal tryptase in 10% mastocytosis patients



Elevated tryptase is present in anaphylaxis and 2 measurements are required to assess baseline



Schwartz et al NEJM 1987 , Gaughey., JACI 2006, Alvarez-Twose et al., Allergy 2012
Schwartz et al., Imm and Allergy Clinics of NA 2006

22y/o male: asthma, allergies, anaphylaxis, abdominal pain, flushing

- Since age 12 severe asthma, allergies, abdominal pain, bloating, diarrhea, flushing, hives CIU, unprovoked anaphylaxis, dizziness, fatigue, hypermobility, joint pain.
- Cannot work a steady job due to HR and dizziness/presyncope during prolonged standing (> 10 min).
- Musician (song named Tryptase)
- Orthostatic cerebral hypoperfusion syndrome (OCHOS)/POTS, small fiber neuropathy and EDS, Tourette syndrome
- Mother and brother with POTS and HαT

Tryptase: 18 ng/ml

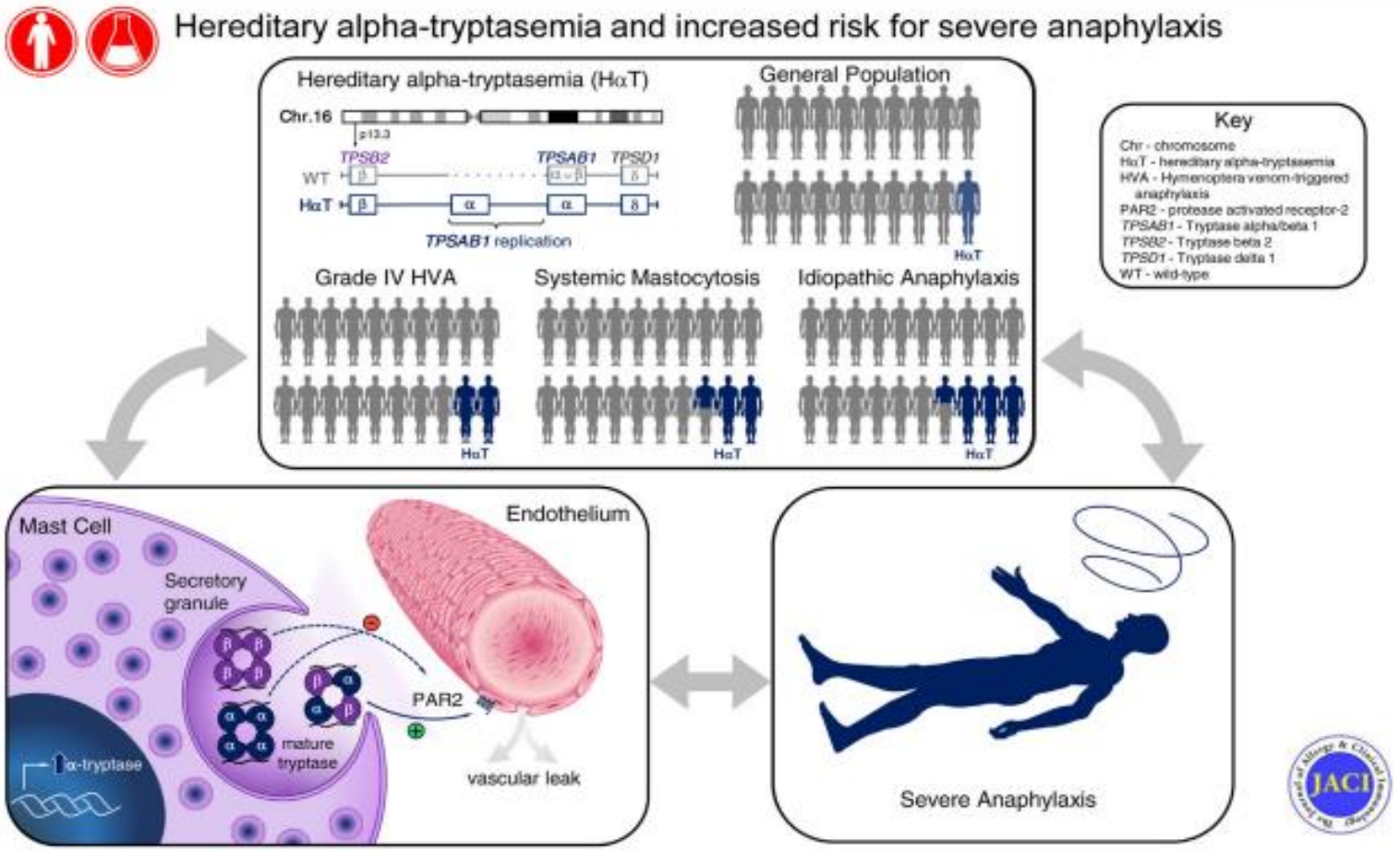
IgE 264 IU/ml , spIgE + wheat, peanut, soy, scallops, cat, dust mites, pollen

Gene-by-Gene: 2α3β beta TPSAB1 gene copies

Heritable risk for severe anaphylaxis associated with increased α-tryptase–encoding germline copy number at *TPSAB1*

Jonathan J. Lyons, MD,[a] Jack Chovanec, BS,[a] Michael P. O'Connell, PhD,[a] Yihui Liu, PhD,[a] Julij Šelb, MD, PhD,[b] Roberta Zanotti, MD,[c] Yun Bai, PhD,[a] Jiwon Kim, BS,[a] Quang T. Le, PhD,[d] Tom DiMaggio, ADN,[a] Lawrence B. Schwartz, MD, PhD,[d] Hirsh D. Komarow, MD,[a] Matija Rijavec, PhD,[b] Melody C. Carter, MD,[a] Joshua D. Milner, MD,[e]* Patrizia Bonadonna, MD,[f]* Dean D. Metcalfe, MD,[a]* and Peter Korošec, PhD[b]*

Bethesda, Md, Golnik, Slovenia, Verona, Italy, Richmond, Va, and New York, NY

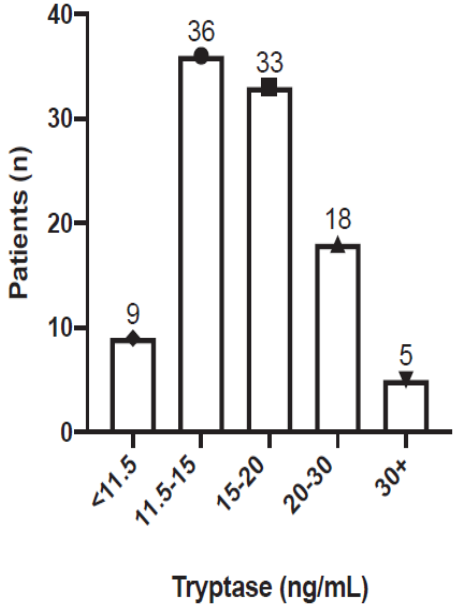


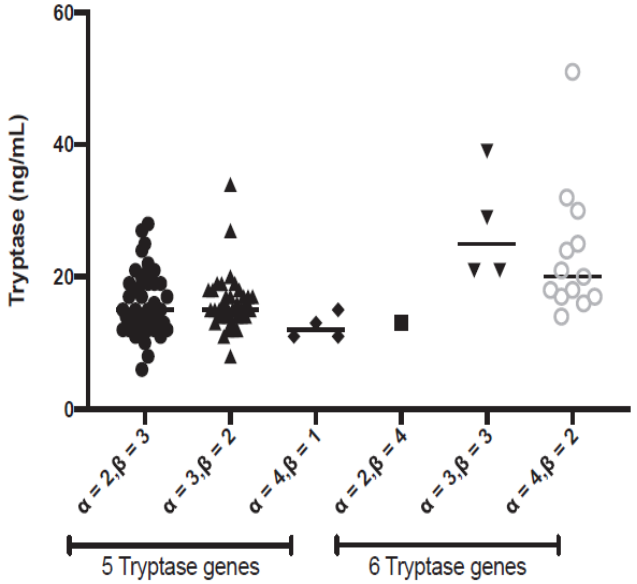
- HαT is the common cause of elevated BST level in Western populations and the first common heritable genetic modifier of anaphylaxis to be described.
- Having concomitant clonal mast cell disease and HαT is associated with greater likelihood of severe anaphylaxis.
- α/β-Tryptase heterotetramers have unique activities that may potentiate immediate hypersensitivity reaction severity.

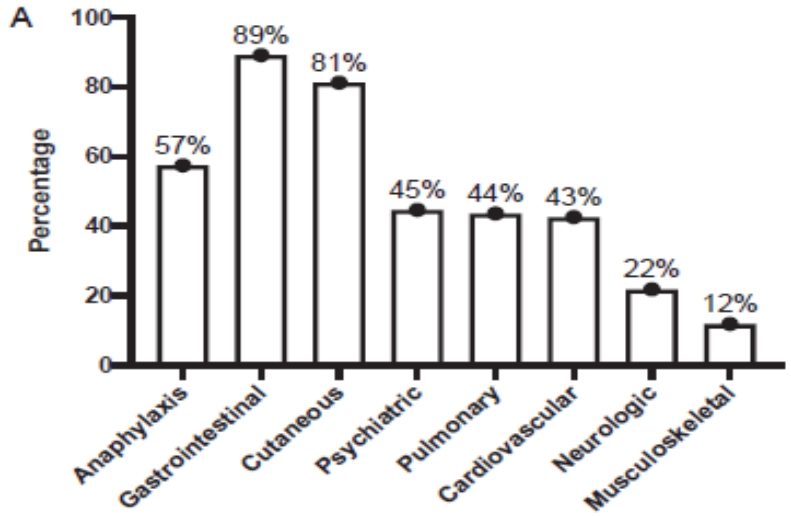
Acute and/or Baseline Tryptase > 8 ng/ml

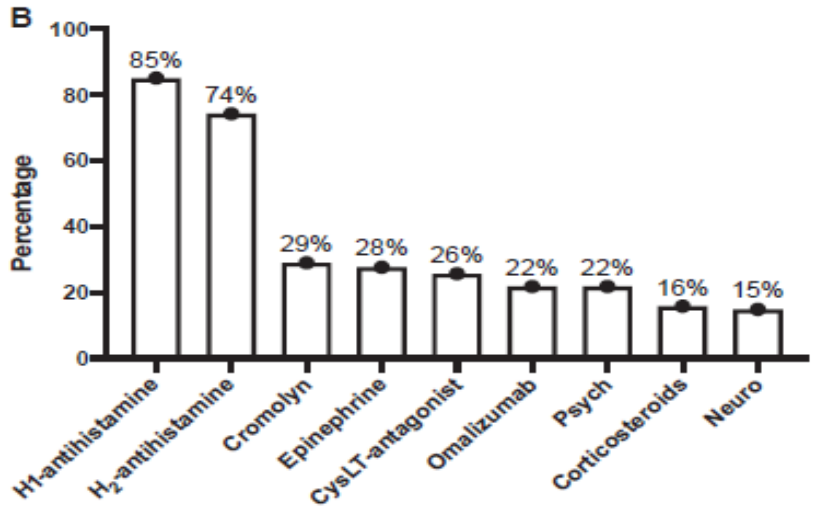
Hereditary alpha-tryptasemia in 101 patients with mast cell activation–related symptomatology including anaphylaxis

Matthew P. Giannetti, MD [*,†]; Emily Weller, BA [*]; Concetta Bormans, PhD [†]; Peter Novak, MD, PhD [§]; Matthew J. Hamilton, MD [†,‖]; Mariana Castells, MD, PhD [*,†]









Bone Marrow Morphologic Findings in Patients with Indolent Systemic Mastocytosis and Hereditary Alpha-Tryptasemia (HαT)

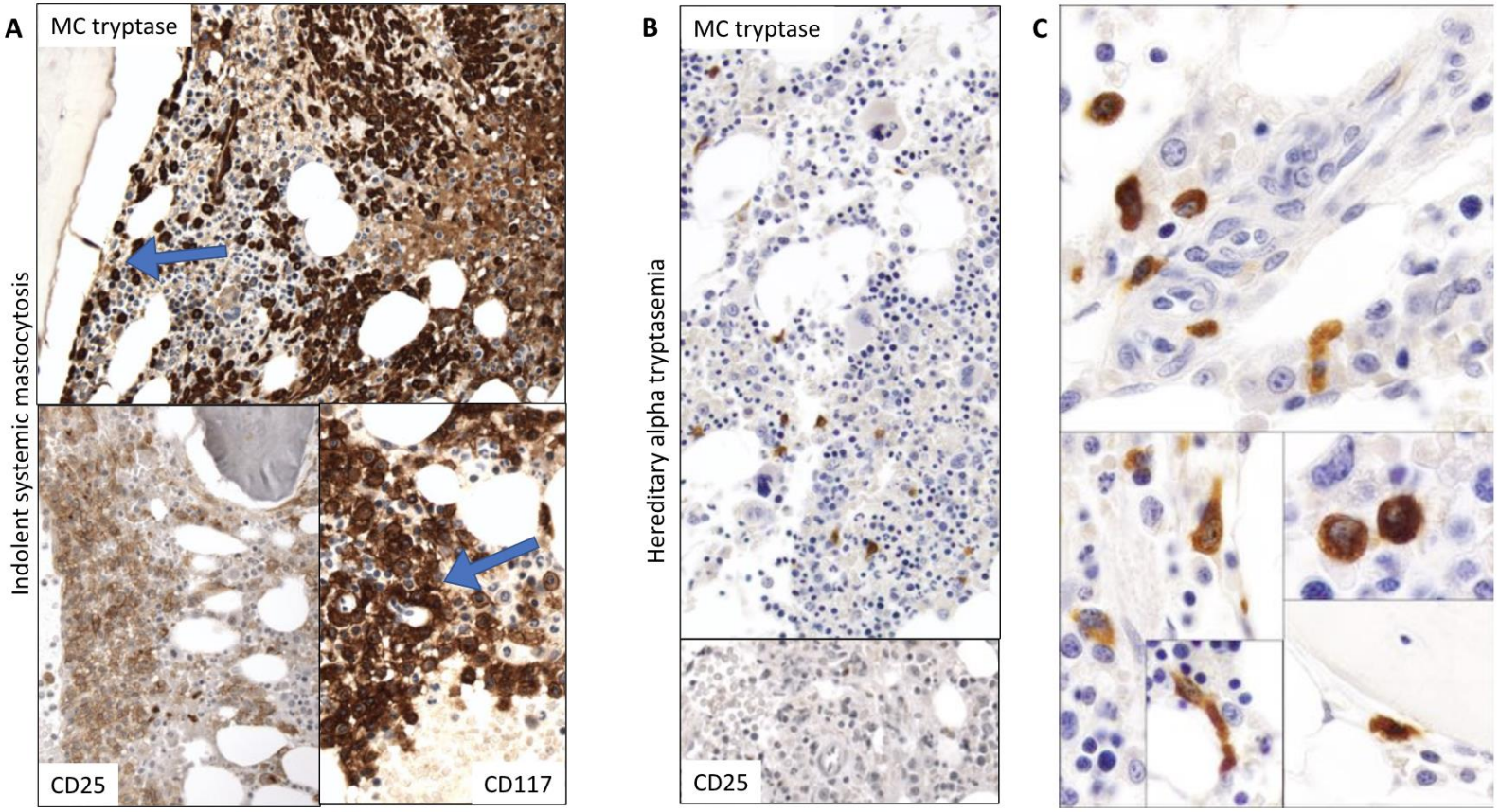


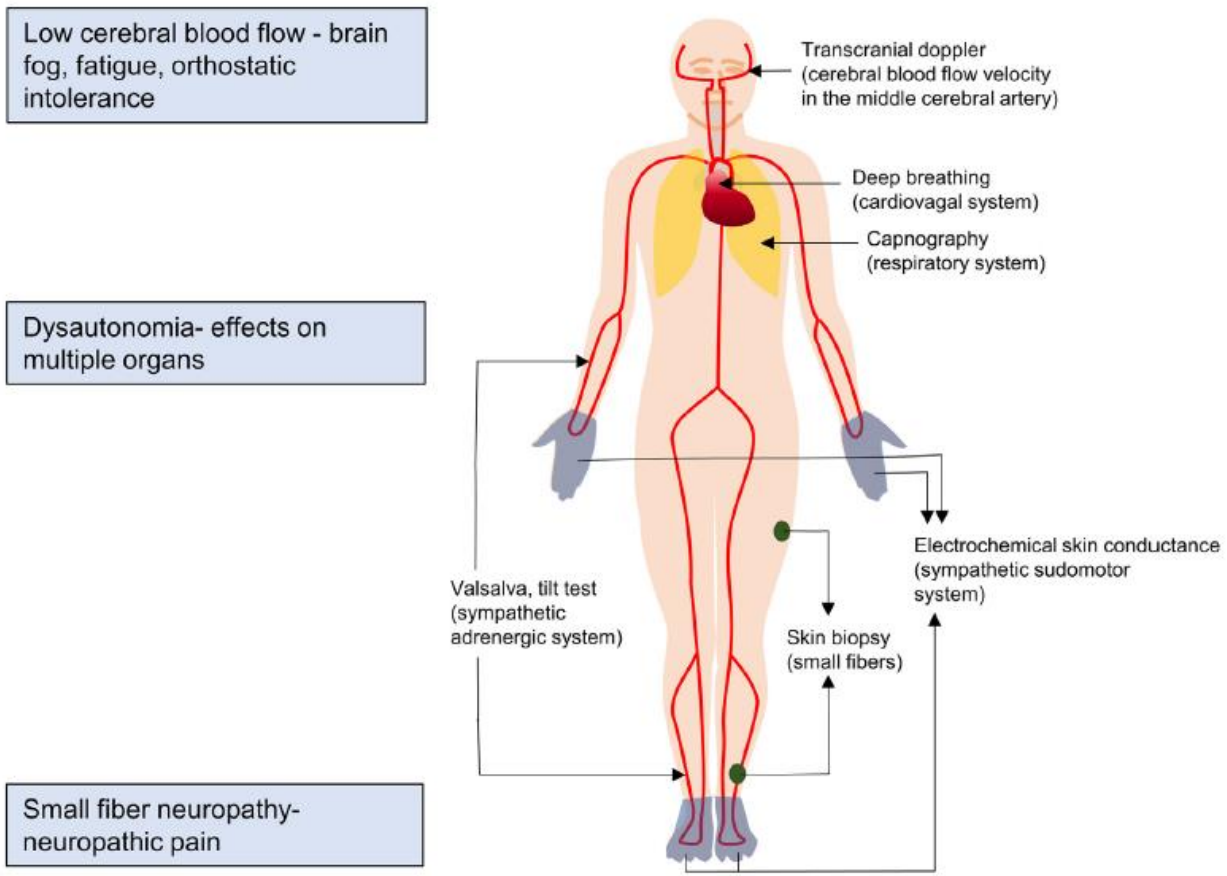
Figure 1

Giannetti MP, Akin C, Hufdhi R, Hamilton MJ, Weller E, van Anrooij B, LyonsJJ, Hornick JL, Pinkus G, Castells M, Pozdnyakova O, Patients with mast cell activation symptoms and elevated baseline serum tryptase have unique bone marrow morphology, Journal of Allergy and ClinicalImmunology (2020)

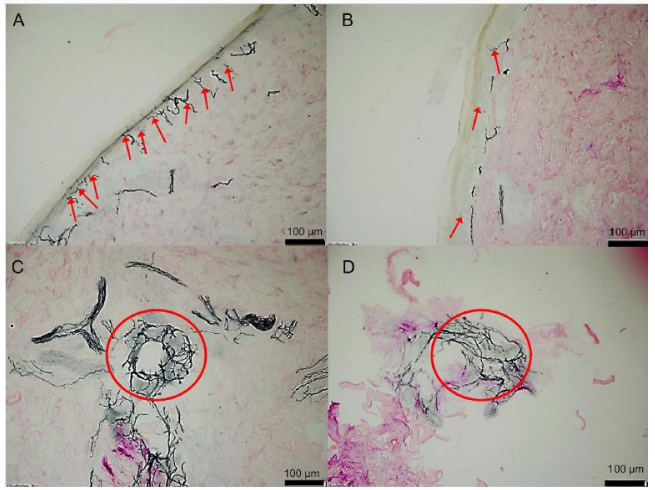
Mast cell disorders are associated with decreased cerebral blood flow and small fiber neuropathy

Peter Novak, MD, PhD[*,†]; Matthew P. Giannetti, MD[†,‡]; Emily Weller, BA[‡]; Matthew J. Hamilton, MD[†,§]; Mariana Castells, MD, PhD[†,‡]

[*] *Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts*
[†] *Harvard Medical School, Boston, Massachusetts*
[‡] *Division of Allergy and Clinical Immunology, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts*
[§] *Division of Gastroenterology, Endoscopy, and Hepatology, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts*



igure 1. The Brigham protocol for comprehensive autonomic testing. The cartoon reveals the specific tests performed and the targeted physiological systems.



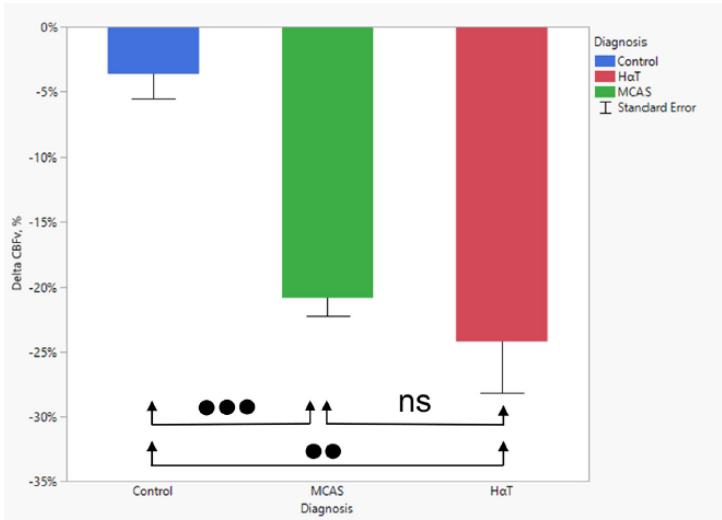


Figure 3. CBFv at the tenth minute of the tilt in the patients with HαT and MCAS compared with controls (••:*P* <.001; •••: *P* <.001; ns, not significant). HαT, hereditary alpha tryptasemia; MCAS, idiopathic mast cell activation syndrome

15 y/o female: hives, dyspnea, headaches, fatigue

- 3 years of flushing, dyspnea; extreme sensitivity to odors, smells, lotions, tobacco smoke; flushing, abdominal bloating, pain, throat tightening, fatigue, hives, intolerance to heat, headaches, food and dye intolerance. Fully functional, tennis school team
- PHM: Asthma, Eczema, SAR on Immunotherapy with anaphylaxis. Received HPV and restarted IT in 2016 and started reacting to foods, developed hives, dizziness/POTS. Very restricted diet (10 foods)
- **Tryptase: 3.7 ng/ml**
- **IgE 38 specific IgE + dust mites, dog**
- **Prostaglandin F2a 14,990 (Nl: < 5000pg/ml Cr)**

Mast Cell Activation Syndrome: A Newly Recognized Disorder with Systemic Clinical Manifestations

TABLE I. Baseline characteristics of patients with MCAS

Characteristic	No. of patients (%)
Sex	
Male	2 (11)
Female	16 (89)
Age (y)	
20-29	1 (6)
30-39	4 (22)
40-49	8 (44)
50-59	5 (28)
Patients with medication allergy	13 (72)
Patients with food allergy and/or environmental allergy	6 (33)
Endoscopy and abdominal imaging before referral	12 (67)
Mean no. of years symptomatic before referral	4.6
Range of years before referral	1-9

Hamilton MJ, Hornick JL, Akin C, Castells MC, Greenberger NJ. 2011 J Allergy Clin Immunol

Non-Clonal Mast Cell Activation Syndrome

TABLE II. Signs and symptoms of patients with MCAS

Sign or symptom	Total (%), n = 18
Abdominal pain	17 (94)
Dermatographism	16 (89)
Flushing	16 (89)
Headache	15 (83)
Poor concentration and memory	12 (67)
Diarrhea	12 (67)
Naso-ocular	7 (39)
Asthma	7 (39)
Anaphylaxis	3 (17)

Patient no.	Total tryptase (ng/mL); normal, 1-15 ng/mL	Mature tryptase (ng/mL); normal, <1 ng/mL	Histamine (nmol/g creatinine); normal, 0-386 nmol/g creatinine	PGD_2 (ng/24 h); normal, 100-280 ng/24 h
1	5.4	<1	380	**511**
2	6.6	<1	—	—
	5.4	<1	**403**	**291**
3	3.1	<1	**1197**	—
4	—	—	**674**	57
	—	—	327	75
5	3.8	<1	236	105
	4.6	<1	**423**	—
	4.2	<1	195	—
	5.6	<1	**486**	—
	4.0	<1	**453**	—
6	4.4	<1	280	**446**
7	15	<1	—	—
	14.4	—	—	—
	12	<1	280	92
	19	—	—	—
8	3.1	<1	76	45
	—	—	**563**	—
9	1.9	**1.9**	60	**297**
10	3.2	<1	—	—
	—	—	46	262
	3.4	<1	—	—
	3.5	**1.4**	—	—
	3.5	**1.2**	—	—
	3.6	**2.8**	66	—
11	2.4	<1	—	—
	3.4	<1	—	—
	2.7	<1	74	**294**
12	—	—	**491**	134
13	3.3	<1	—	—
	—	—	74	**1114**

Elevated mast cell mediators in 100% of patients either at baseline or during episodes

All responded to medications

Overview of differential diagnoses mimicking mast cell activation and mast cell activation syndrome

	Drug exanthema
	Atopic or contact dermatitis
Gastrointestinal	Inflammatory bowel disease
	Food intoxication (eg, scombroid fish poisoning)
	Irritable bowel syndrome
	Eosinophilic esophagitis or gastroenteritis
	Gastrointestinal motility disorders
	Vasoactive intestinal peptide-secreting tumor (VIPoma)
Cardiovascular	Arrythmias
	Myocardial infarction
	Endocarditis/endomyocarditis
	Aortic stenosis with syncope
	Pulmonary embolism
Neuropsychiatric	Seizures
	Stroke
	Multiple sclerosis
	Dysautonomia (eg, postural tachycardia syndrome)
	Vasovagal syncope
	Panic attacks and anxiety conditions

Castells, Escribano, Metcalfe

Triggers

Physical stimuli

- Frequent
- Heat
- Sudden changes of temperature
- Rubbing/pressure of skin lesions (Darier's sign may induce hypotension)
- Scalp trauma (children with scalp involvement)
- Infrequent
- Cold
- Sunlight

Emotional factors

Frequent
Stress,
Anxiety
Sleep deprivation

Infectious diseases with fever

- Viral (URTI)
- Bacterial (bronchitis, pneumonia)

Drugs

- Non-steroidal anti-inflammatory drugs *
- Morphine and derivatives
- Cough medication: dextromethorphan, dymemorphan

Miscellaneous

- Dentition
- Vaccines
- Surgery

Associated allergic diseases **/***

1. Responses greatly vary from patient to patient.
2. Patients with known sensitivities must wear a Medic alert bracelet or necklace.

* 2/92 cases (ref.) If patients have not taken these drugs before, provocation test may be performed under close medical supervision.

**The prevalence of allergic diseases in pediatric mastocytosis is 27% {Gonzalez de, 2007 15409 /id}

*** Foods, environmental allergens and other factors may exacerbate or precipitate mast cell activation in mastocytosis patients.

TABLE II. Approach to mast cell mediator–induced symptoms in mastocytosis and MCAS.

A. Avoidance of triggers: patient specific
Specific foods, medications (NSAIDs, vancomycin, quinolones), environmental allergens, and general triggers (stress, lack of sleep, emotions)
Physical triggers (exercise, rubbing, pressure)
Changes in temperature (heat, cold)
Extreme temperatures
Dryness of skin
B. Premedications recommended for surgery, invasive procedures (endoscopy, colonoscopy, others), radiological procedures with contrast dyes, dental procedures, and vaccinations: 12 and 1 h
• Antihistamine receptors H1 and H2
• Leukotriene blocker
• Steroid (0.5-1 mg/kg)
C. Management of cutaneous mastocytosis:
Local care of skin
Skin moisturizer
Water-soluble sodium cromolyn cream/ointment (1% to 4%)
Avoid friction, pressure, and temperature changes
Consider surgical excision for mastocytomas (flexures, soles, palms, scalp)
Steroid creams
PUVA (psoralens)

Mast Cell Activation Syndrome and Mastocytosis: Initial Treatment Options and Long-Term Management

JACI In Practice 2019

Mariana Castells, MD, PhD[a], and Joseph Butterfield, MD[b] *Boston, Mass; and Rochester, Minn*

Personalized Medicine

Targeting Mediators and Symptoms

Mast Cell Activation Syndrome and Mastocytosis: Initial Treatment Options and Long-Term Management

Mariana Castells, MD, PhD[a], and Joseph Butterfield, MD[b] *Boston, Mass; and Rochester, Minn*

Anaphylaxis	
Acute	Epinephrine IM 0.3-0.5 mg
	Corticosteroids (0.5-1 mg/kg) X1 dose
	IV fluids
	Antihistamine receptors H1 and H2
Prevention	H1-blockers and H2-blockers
	Leukotriene blockers
	Corticosteroids 0.5-1 mg/kg
	Omalizumab 300 mg every 28 days
Hymenoptera-induced	Venom immunotherapy
	Omalizumab 300 mg every 28 days
Naso-ocular: nasal stuffiness, nasal pruritus, conjunctival injection	H1-blockers (as per above)
	Inhaled corticosteroids
	Nasal cromolyn sodium
Bone: osteopenia, osteoporosis, bone fractures	Calcium, Vit D
	Biphosphonates
	Clodronate, pamidornate, alendronate, zolendronate
	Interferon alpha 2a

NCCN 2022

STEPWISE PROPHYLACTIC TREATMENT APPROACH FOR CHRONIC MAST CELL MEDIATOR-RELATED SYMPTOMS

Organ Involvement/Symptoms	Stepwise Treatment[d,e]
Skin: Pruritus, flushing, urticaria, angioedema dermatographism	1. H1 blockers and H2 blockers 2. Leukotriene receptor antagonist 3. Aspirin 4. Ketotifen[c] 5. Topical cromolyn sodium (cream/ ointment 1%–4%)[c]
Gastrointestinal: Diarrhea, abdominal cramping, nausea, vomiting	1. H2 blockers 2. Cromolyn sodium 3. Proton pump inhibitors 4. Leukotriene receptor antagonist 5. Ketotifen[c]
Neurologic: Headache, poor concentration and memory, brain fog	1. H1 blockers and H2 blockers 2. Cromolyn sodium 3. Aspirin 4. Ketotifen[c]
Cardiovascular: Pre-syncope, tachycardia	1. H1 blockers and H2 blockers 2. Corticosteroids 3. Omalizumab
Pulmonary: Wheezing, throat swelling	1. H1 blockers and H2 blockers 2. Corticosteroids 3. Omalizumab
Naso-ocular: Nasal stuffiness, nasal pruritus, conjunctival injection	1. H1 blockers 2. Corticosteroids 3. Cromolyn sodium

NCCN 2022

ACUTE TREATMENT OF ANAPHYLAXIS[1-7]
(Includes hymenoptera venom anaphylaxis)

Indication	Treatment
Systemic hives	Antihistamines (H1 blockers and H2 blockers)
Systemic hives + second organ involved in an acute onset reaction (eg, upper/lower airway, gastrointestinal, neurologic, cardiovascular)	Epinephrine intramuscular (IM) (repeat up to 3 times every 5 minutes in the absence of clinical improvement) IV Epinephrine after 3 doses of epinephrine IM
Acute onset of anaphylaxis with the following symptoms: • Hypotension • Laryngeal edema • Vasomotor collapse • Oxygen desaturation • Seizures	Epinephrine (IM) (repeat up to 3 times every 5 minutes in the absence of clinical improvement) IV Epinephrine after 3 doses of epinephrine IM
Complementary treatments (in addition to antihistamines) • IV fluids • Oxygen • Consider glucagon (if anaphylaxis related to β-adrenergic receptor blockade) • Antihistamines such as diphenhydramine (25 mg every 2–4 h up to 100 mg/24 h) should be considered before starting corticosteroid therapy • Corticosteroids (0.5–1 mg/kg) • Consider bradykinin inhibitor (if anaphylaxis due to ACE inhibitor)	

PREVENTION OF ANAPHYLAXIS[1-7]

Indication	Treatment
• Hymenoptera-specific IgE or skin test positive	Venom immunotherapy Rush desensitization (may be available only in selected centers)
• Unprovoked anaphylaxis • Hymenoptera or food-induced, with negative specific IgE or negative skin test • To improve tolerance while on immunotherapy	Omalizumab[8-10]

TREATMENT FOR OSTEOPENIA/OSTEOPOROSIS[11,12]

- Supplemental calcium and vitamin D
- Bisphosphonates (with continued use of antihistamines)
  - May resolve bone pain and improve vertebral bone mineral density (more than femoral head bone mineral density)
- Peginterferon alfa-2a
  - Consider for patients with refractory bone pain and/or worsening bone mineral density on bisphosphonate therapy
- Anti-RANKL monoclonal antibody (eg, denosumab)
  - Generally used as second-line therapy for patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphophonates because of renal insufficiency
- Vertebroplasty/kyphoplasty for refractory pain associated with vertebral compression fractures in selected patients

NCCN 2022

SPECIAL CONSIDERATIONS FOR THE MANAGEMENT OF PATIENTS WITH SYSTEMIC MASTOCYTOSIS

Pregnancy[6-15]

- Based on a paucity of studies, insufficient evidence currently exists regarding whether a diagnosis of SM results in significantly increased rates of adverse maternal or fetal outcomes (eg, spontaneous miscarriage, preterm infants, complications of labor and delivery) compared to the general population.
- A diagnosis of SM does not appear to affect fertility.
- Pre-conception, pregnancy, and the peripartum period should be managed by a multidisciplinary team, including high-risk obstetrics, anesthesia, and allergy.
- Management of SM during pregnancy involves alleviation of symptoms related to mast cell activation and titration of acceptable medications to minimize potential harm to the fetus.
- Avoidance of triggers, prophylactic use of antihistamines, as-needed corticosteroids, and epinephrine on demand for anaphylaxis are standard approaches during pregnancy. Please refer to the table for medications used to treat mastocytosis and their potential risks during both pregnancy and lactation (SM-K 3 of 4).
- For severe cases of SM during pregnancy refractory to conventional therapy, cytoreductive therapy with peginterferon alfa-2a can be considered. Use of cladribine or tyrosine kinase inhibitors (eg, imatinib, midostaurin, avapritinib) is not recommended. There are not sufficient data to establish the use of peginterferon alfa-2a (risk category C) in pregnancy. It should be used only if benefits outweigh potential risk to the fetus.[15]

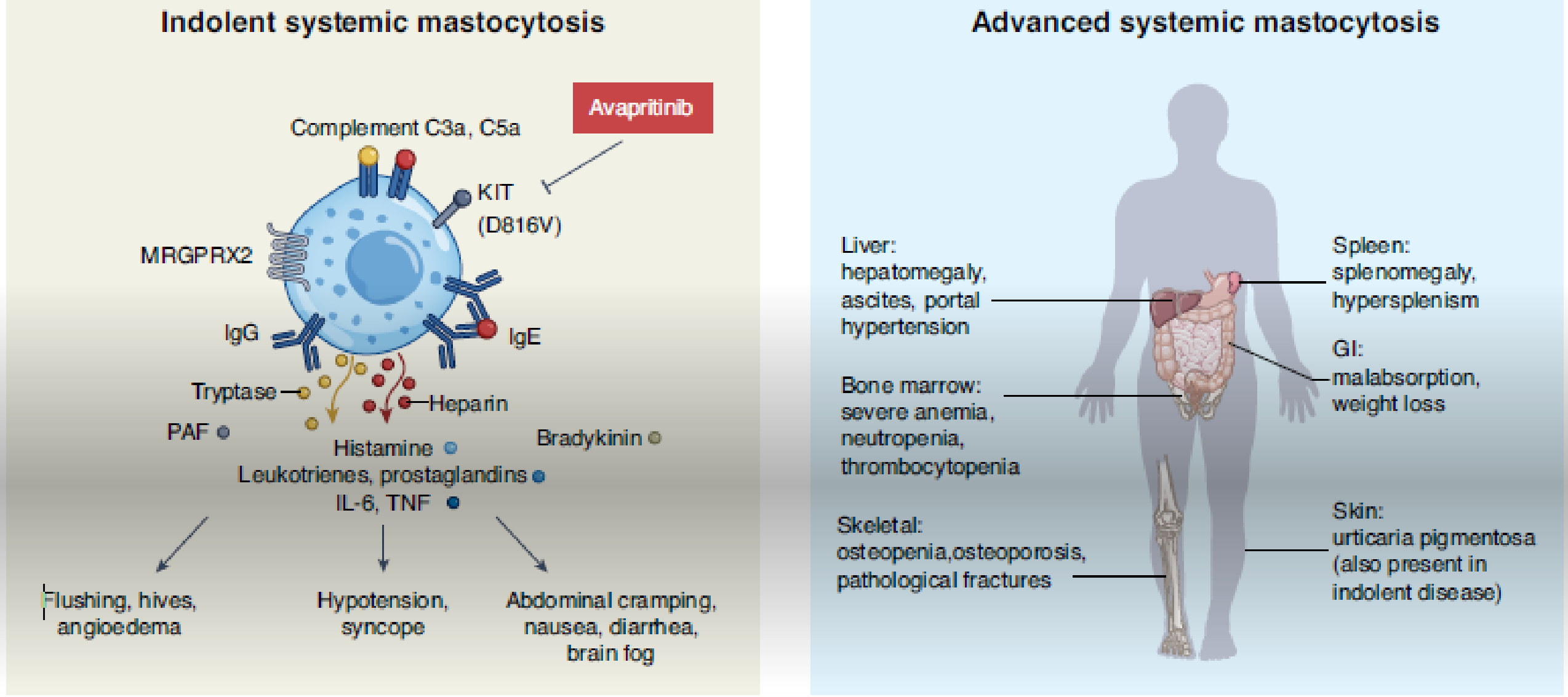


Fig. 1 | SM symptoms, mediators and organ impact of indolent and advanced disease. MRGPRX2, G protein–coupled receptor; IgG and IgE, immunoglobulins; PAF, platelet-activating factor; IL-6, interleukin 6; TNF, tumor-necrosis factor; GI, gastrointestinal.

Recent Publications

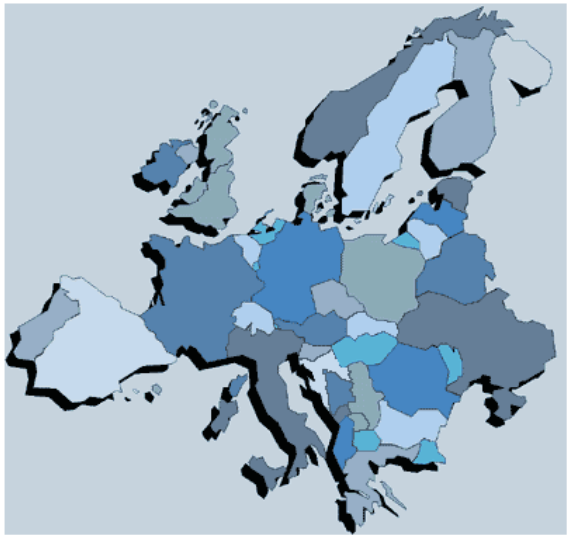
- Giannetti MP, Weller E, Alvarez-Twose I, Torrado I, Bonadonna P, Zanotti R, Dwyer DF, Foer D, Akin C, Hartmann K, Rama TA, Sperr WR, Valent P, Teodosio C, Orfao A, Castells M. **COVID-19 infection in patients with mast cell disorders including mastocytosis does not impact mast cell activation symptoms**. J Allergy Clin Immunol Pract. 2021 Feb 23:S2213-2198(21)00203-8. doi: 10.1016/j.jaip.2021.02.023
- Hamilton MJ, Zhao M, Giannetti MP, Weller E, Hufdhi R, Novak P, Mendoza-Alvarez LB, Hornick J, Lyons JJ, Glover SC, Castells MC, Pozdnyakova O. **Distinct Small Intestine Mast Cell Histologic Changes in Patients With Hereditary Alpha-tryptasemia and Mast Cell Activation Syndrome**. Am J Surg Pathol. 2021 Jan 20. doi: 10.1097/PAS.0000000000001676.
- Giannetti MP, Weller E, Bormans C, Novak P, Hamilton MJ, Castells M. **Hereditary alpha-tryptasemia in 101 patients with mast cell activation-related symptomatology including anaphylaxis.** Ann Allergy Asthma Immunol. 2021 Jan 17:S1081-1206(21)00024-7. doi: 10.1016/j.anai.2021.01.016.
- Giannetti MP, Akin C, Hufdhi R, Hamilton MJ, Weller E, van Anrooij B, Lyons JJ, Hornick JL, Pinkus G, Castells M, Pozdnyakova O. **Patients with mast cell activation symptoms and elevated baseline serum tryptase level have unique bone marrow morphology**. J Allergy Clin Immunol. 2020 Nov 25:S0091-6749(20)31633-X. doi: 10.1016/j.jaci.2020.11.017.
- Rama TA, Moreira A, Castells M. **mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis**. J Allergy Clin Immunol. 2021 Mar;147(3):877-878. doi: 10.1016/j.jaci.2021.01.004
- *Novak P, Giannetti MP, Weller E, Hamilton MJ, Castells M. **Symptomatic Hereditary Alpha Tryptasemia and Idiopathic Mast Cell Activation Syndrome 2 Patients Present with Decreased Cerebral Blood Flow, Small Fiber Neuropathy, and Autonomic Dysfunction** Annals Oct 2021

Brigham and Women's Hospital Hale Building for Transformative Medicine Mastocytosis Center

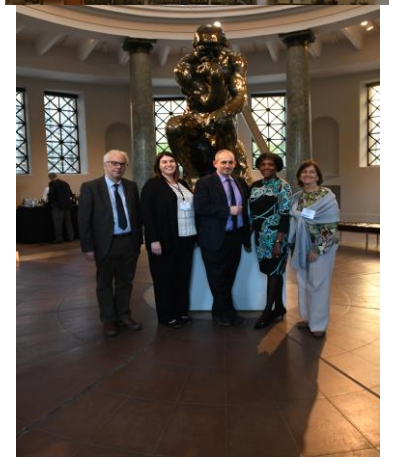
- **Mariana Castells**
- **Matthew Giannetti**
- **Tara Saco**
- **Matthew Hamilton**
- **Jennifer Nicoloro-Santa Barbara**
- Richard Horan
- Daniel de Angelo
- Jason Hornick
- Olga Pozdnyakova
- Peter Novak
- Nora Barrett
- Daniel Dwyer
- **K Frank Austen (emeritus)**

The European Competence Network on Mastocytosis – ECNM

The European Competence Network on Mastocytosis, ECNM, is a 'non-profit' cooperative initiative of a group of scientists and clinicians in Europe who are devoted to merge their efforts in an attempt to improve recognition, diagnosis, and therapy in patients with mastocytosis.



Specific aims in the ECNM are to provide the best available information for patients and doctors, to provide access to important diagnostic tests for all patients, to establish standards for the diagnosis and treatment of mastocytosis, to establish Reference Centers and Centers of Excellence in Europe, and to facilitate referrals to specialists in these centers for all patients, either through doctor-doctor telenet-contact, or direct referral if required.



American Initiative in Mast Cell Diseases

2022 CONFERENCE • SALT LAKE CITY, UT

The 2022 American Initiative in Mast Cell Diseases (AIM) Physician and Investigator Conference will be held at the Little America Hotel in downtown Salt Lake City, Utah, May 21–22, 2022, and will feature cutting-edge research in mast cell disease presented by expert faculty in mast cell disease management.

K. Frank Austen Lifetime Achievement Award

The 2022 AIM Physician and Investigator Conference is delighted to announce Professor Dr. Peter Valent from the Medical University of Vienna in Austria as the recipient of the K. Frank Austen Lifetime Achievement Award for outstanding contributions to the study of mast cell diseases/mastocytosis.

Professor Valent's accomplishments span several decades and include the establishment of international consensus criteria for the diagnosis and classification of mastocytosis/mast cell activation syndrome, laboratory investigations of the biology of mast cells, preclinical characterization of novel mast cell-directed therapies, and the creation of the European Competence Network on Mastocytosis (ECNM), a model for AIM. Professor Valent's leadership has been the driving force behind numerous collaborations that have catalyzed bench-to-bedside progress for the benefit of patients with mast cell diseases. Professor Valent is the second recipient of the award after it was bestowed on its namesake, Professor K. Frank Austen, at the inaugural AIM meeting at Stanford University School of Medicine in 2019.

As part of the award ceremony, Professor Valent will deliver the keynote lecture, entitled, "A Metachromatic Career: Looking Back to Inform Future Priorities in Mast Cell Disease" on Saturday, May 21, 2022, at our Salt Lake City meeting. Please join us in honoring Professor Valent's seminal contributions to the field of mast cell diseases.

Registration Is Now Open

Registration is open for the 2022 AIM Conference, with options for in-person and virtual participation.

Learn more about the event and request a registration invitation. Registration is open to physicians and researchers. Pharmaceutical representatives will have limited attendance, based on sponsorship.

AIM 2022 Program Committee

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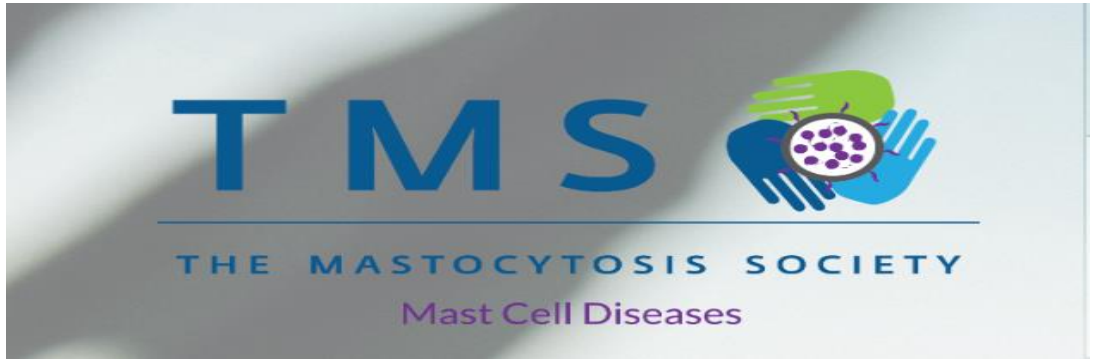
Mariana Castells, MD, PhD
Brigham and Women's Mastocytosis Center

Melody Carter, MD
National Institute of Health

Accreditation: The University of Utah School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

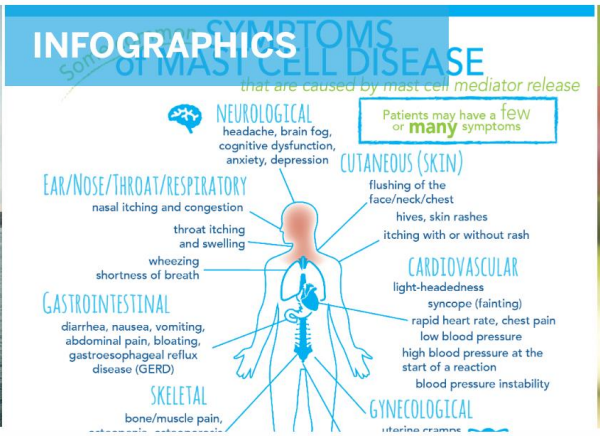


The Mastocytosis Society

is a non-profit organization dedicated to supporting patients affected by Mastocytosis and Mast Cell Activation Diseases as well as their families, caregivers and physicians through research, education and advocacy.

LEARN MORE >

THE MASTOCYTOSIS SOCIETY



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