Australian Chronic Infectious and Inflammatory Disease Society

Inaugural Meeting

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Mast Cell Activation Disease: Current Concepts

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Learning Objectives & Disclaimers

- Learning Objectives
  - Review basic concepts regarding mast cell activation disorders (MCAD, including mast cell activation syndrome (MCAS))
  - Review clinical presentation of MCAS
  - General approach to diagnosis and treatment of MCAS
- Conflicts of Interest
  - None
- Note that there are not yet any FDA-approved treatments for MCAS, and not even (yet) any "well-designed, non-randomized clinical trials," let alone (yet) any "high-quality randomized controlled clinical trials" (there just hasn't been time yet for such trials!), so by definition, all treatment options discussed in this presentation are ACCME Level Of Evidence (LOE) "C" ("consensus viewpoint or expert opinion").

Outline

- What is mast cell activation disease (MCAD)?
  - What we've long known:
    - Allergic diseases.....
    - Mastocytosis.....
  - What's new:
    - Mast cell activation syndrome (MCAS).....
      - Basic behavior of the disease
      - Clinical presentation
      - General approach to diagnosis and treatment
  - Research issues

	General Clinical Theme
Allergic diseases.....	Allergy ± Inflammation
Mastocytosis.....	MC Neoplasia ± Allergy ± Inflammation
Mast cell activation syndrome (MCAS).....	Inflammation ± Allergy ± Aberrant Growth (Dystrophism)

Three ~~Two~~ cases…

“Polycythemia vera”

“Pure red cell aplasia”

and “Burning Mouth Syndrome”?

"Polycythemia vera"

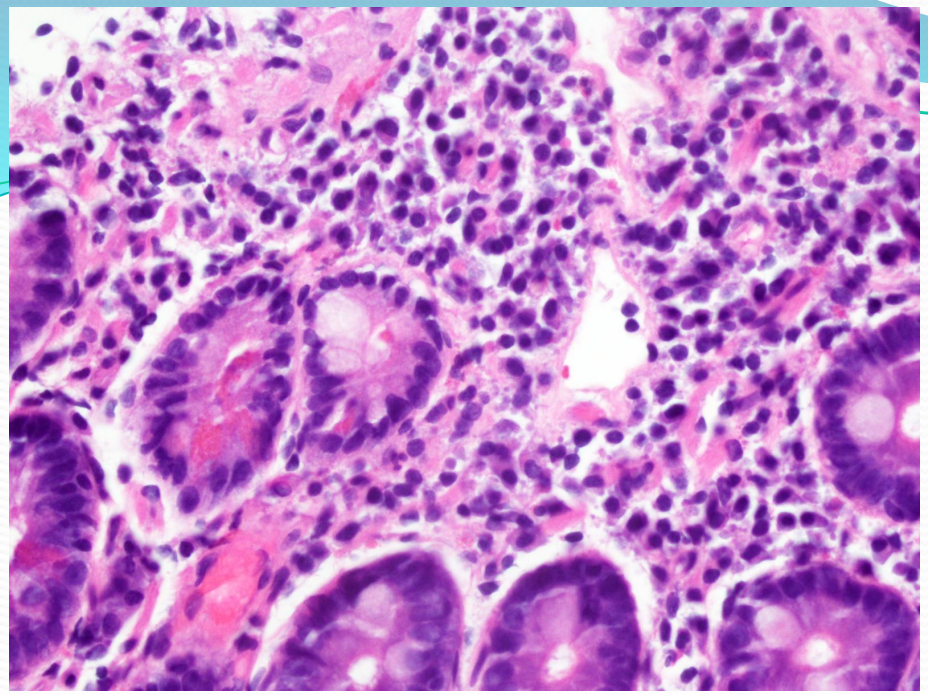
- 1980s: healthy 30ish woman notices migratory rash
- Over time: fatigue, itching, vertigo, falls; evals negative
- 2005: mildly elevated hemoglobin; polycythemia vera (PV) diagnosed (incorrectly), standard therapy begun
- Steadily worsened (migratory GI symptoms, labile BP/pulse ("POTS"), poor healing, episodic shortness of breath, frequent upper respiratory "infections" with no infectant ever found, rashes to all antibiotics), had to close her business
- 2008: self-referred for further eval

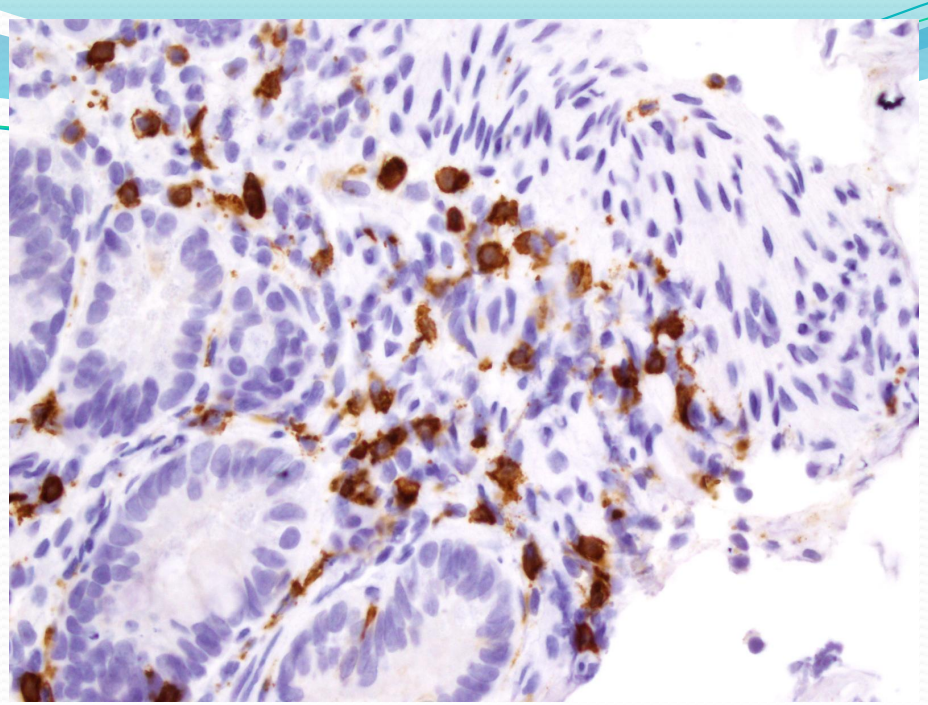
Afrin LB. Polycythemia from Mast Cell Activation Syndrome: Lessons Learned. *Am J Med Sci* 2011;342:44-49.

"Polycythemia vera"

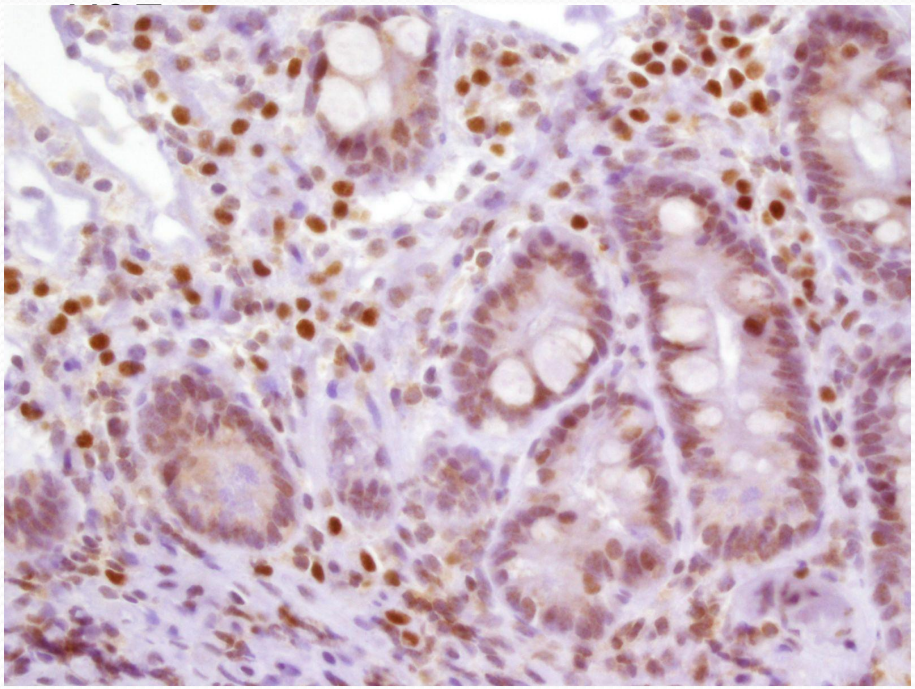
- No sleep apnea, no relevant family/social/medication history
- Exam: looked tired, nothing else
- Doesn't fit PV; what else is driving her issues including ↑hemoglobin?
  - Extensive additional testing proves she doesn't have PV – and fails to find any other known cause of ↑hemoglobin
- Possible fit with mastocytosis; is that what it is?
  - No?: serum tryptase, urine N-methylhistamine normal; marrow and rash biopsies show no mastocytosis
  - Yes?: sl. ↑ urinary prostaglandin D_2
  - EGD/colonoscopy: normal, but biopsies taken anyway…
  - …all "textbook normal" on H&E, but on IHC…

Afrin LB. Polycythemia from Mast Cell Activation Syndrome: Lessons Learned. *Am J Med Sci* 2011;342:44-49.





CD117
40x



CD25
40x

- Dx: “atypical mastocytosis”?
- Low-dose imatinib begun
  - 100 mg/d x 1 week, then
  - 200 mg/d
- The first week: tolerated fine, but no response
- And then, on waking the morning after the fourth dose of 200 mg.....

“Polycythemia vera”

- All symptoms acutely gone.
- Improvement sustained >12 years now.
- All labs normalized.
- Resumed exercise and full-time work.

Afrin LB. Polycythemia from Mast Cell Activation Syndrome: Lessons Learned. *Am J Med Sci* 2011;342:44-49.

"Pure Red Cell Aplasia"

- 2004: 50ish woman, worsening fatigue; severe anemia
- Dx: idiopathic pure red cell aplasia (PRCA, confirmed)
- Refractory to all standard treatments for PRCA
- Needing 3 units of blood every 2-3 wks to maintain merely half-normal hemoglobin (Hgb) level
- 2009: 6th opinion: ROS pan-⊕, $uPGD_2$ ↑↑↑, Dx: "MCAS"
- Antihistamines: Good Hgb ↑ in 4 weeks, no transfusions
- Imatinib 200 mg/d added: Hgb normalized in 6 weeks
- "PRCA" relapsed 1 yr later
  - Tried cromolyn (previously precluded by insurer): remission again in 4 wks

Afrin LB. Pure red cell aplasia masquerading as mast cell activation disorder. *Int J Hematol* 2010 Jun; 91:907-908.

"Burning Mouth Syndrome"

- 2004: 50ish woman, new constant "burning" pain throughout GI tract, pain score 10/10 in mouth
- Very extensive evaluations over a year all negative except for finding mild chronic stomach inflammation and, finally, a 100-fold elevated serum chromogranin A (CgA) (not on PPIs)
- Neuroendocrine (NE) malignancy?
  - Miserable from pain, but didn't look like she had cancer of any sort
  - Extensive cancer search negative
  - Top five U.S. NE cancer experts consulted
    - Unanimous opinion: ↑↑CgA must be due to NE cancer, keep looking
- MC disease?
  - Blood/urine markers normal; marrow, oral mucosa biopsies normal

Afrin LB. Burning Mouth Syndrome and Mast Cell Activation Disorder. *Oral Surg Oral Med Oral Path Endodontol* 2011;111:465-472.

"Burning Mouth Syndrome"

- Early '09: Revisited old gastric biopsy with CD117 staining, showing ↑↑MCs (but not in pattern suggestive of mastocytosis)
- Dx: mast cell activation syndrome (MCAS)
- Antihistamines/NSAIDs: Pain ↓ to 1/10 overnight
- MCAS found in every subsequent "idiopathic" BMS patient I've examined
  - Different abnormal MC mediator patterns in blood/urine in different patients
  - ↑MCs in GI tract biopsies when checked
  - All responding to various MC-targeted therapies

Afrin LB. Burning Mouth Syndrome and Mast Cell Activation Disorder. *Oral Surg Oral Med Oral Path Endodontol* 2011;111(4):465-472.

Highly divergent presentations, but…

- …same root disease?
- How can “one disease” (MCAS) do this?
- Could other “weird” presentations be possible?

But hold on a second. Before talking more about this “new” mast cell disease, let’s back up to look at what we’ve long known about diseases of the mast cell…

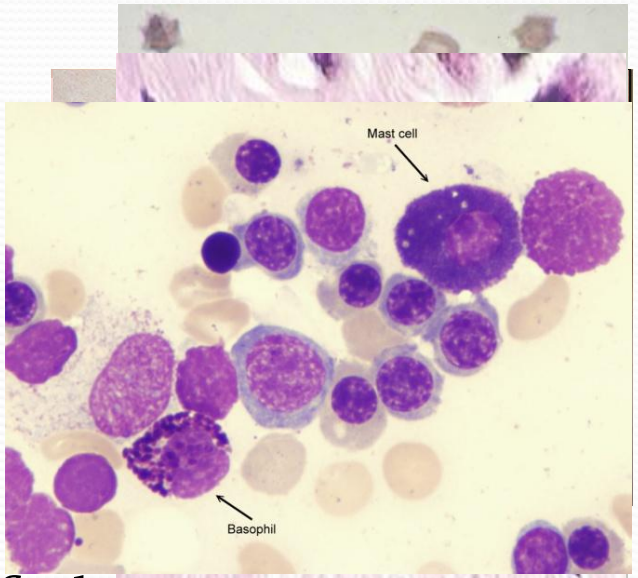
Allergic Diseases

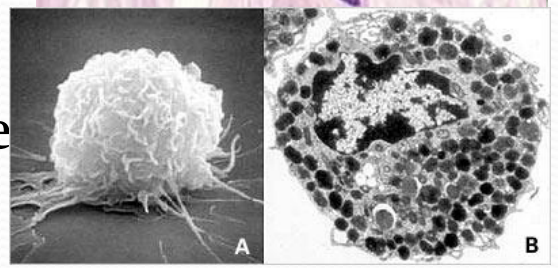
- Allergy, asthma, angioedema, urticaria, anaphylaxis
- 2013: 700 million suffer allergic diseases worldwide
  - 10% of preschoolers worldwide now have food allergies
- Steadily increasing incidence/prevalence across all ages
  - e.g., China (prevalence): 1999: 3.5%; 2009: 7.7%
  - Greatest increases in children < 5 years old
- Allergic diseases are conditioned by a number of genes and influenced by environmental factors
  - Incidence of allergic disease in children if…
    - …neither parent suffers allergic disease: 5-15%
    - …only one parent suffers allergic disease: 20-40%
    - …both parents suffer allergic disease: ≥ 60%
- Relatively little mortality, but significant QoL effects

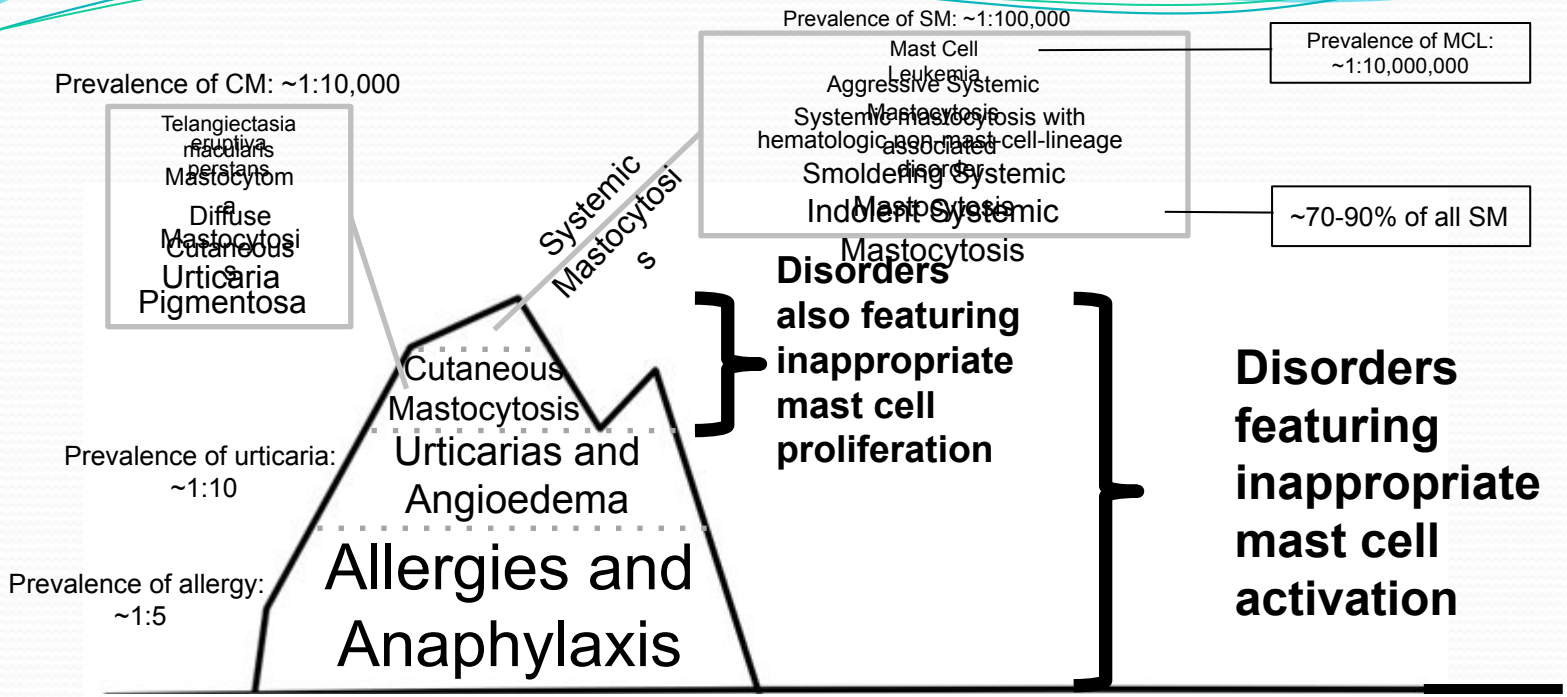
1. Prescott SL et al. A global survey of changing patterns of food allergy burden in children. World Allergy Organiz J 2013;6:21, pp. 1-12.
2. Pawlinska-Chmara R et al., Effect of Socio-Economic Status on Quality of Life in People Affected with Respiratory Allergy, pp. 385-392, in M. Pokorski (ed.), *Neurobiology of Respiration*, Advances in Experimental Medicine and Biology 788, DOI 10.1007/978-94-007-6627-3_52, Springer Science+Business Media Dordrecht 2013.

Mastocytosis: A Long History

- 1869: Urticaria pigmentosa (UP) first described
- 1877: First description of the *mastzelle*
- 1887: UP linked with *mastzelles*
- 1933: Suggestion of linkage with internal dz
- 1939: MC heparin identified
- 1949: Definitive linkage with systemic dz
- 1953: MC histamine identified
- 1984: First conception "MCAS" might exist
- 1987: MC tryptase identified
- 1988: Travis classification
- 1995: KIT activating mutation D816V identified
- 1998: Unique flow cytometric signature found
  - CD117 + (CD25 and/or CD2)
- 2001: WHO classification and imatinib
- MC <u>neoplasia</u> is morbid only in rare, aggressive forms; MC <u>activation</u> is what causes symptoms







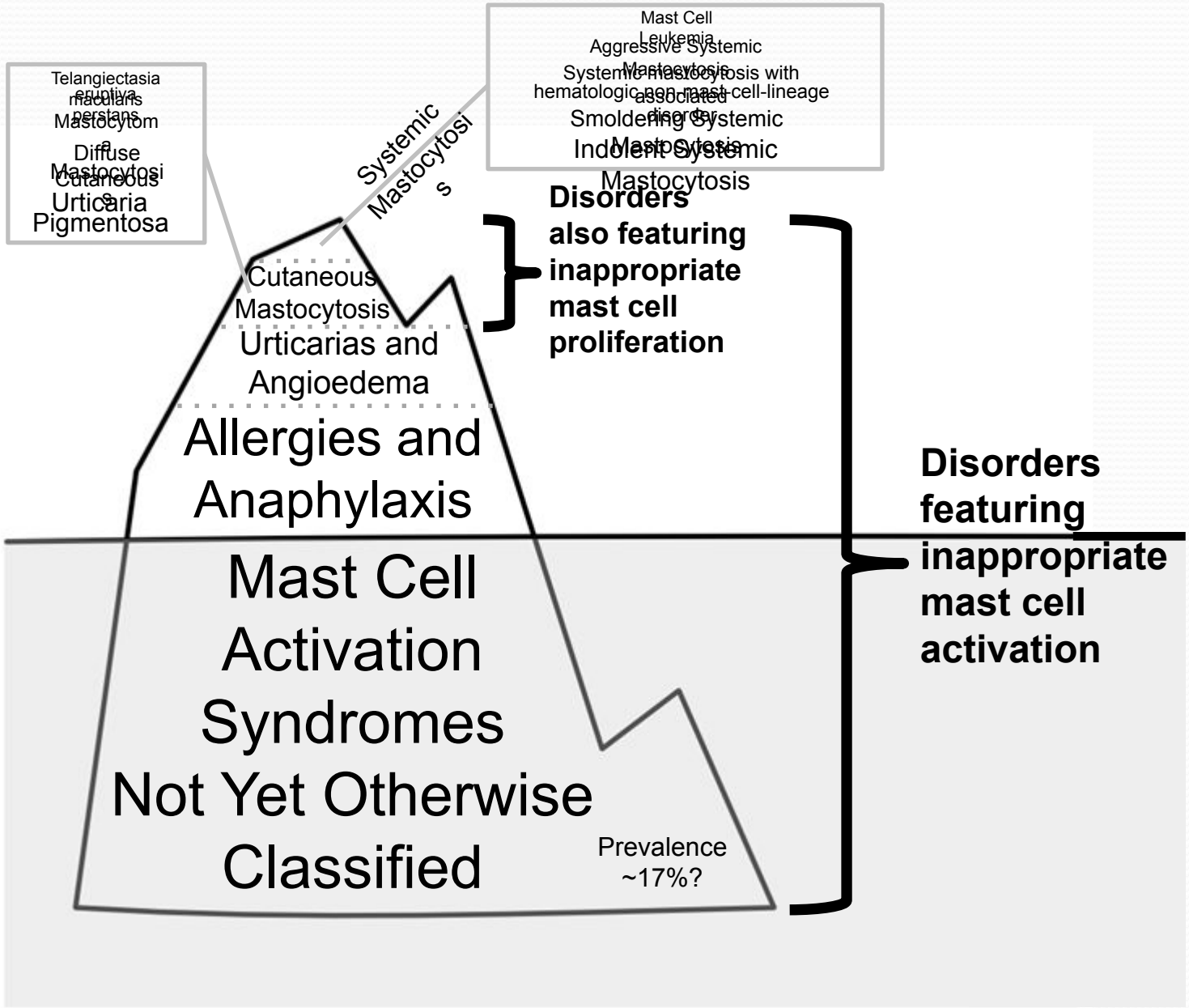
The Spectrum of Mast Cell Disease We've Long Known

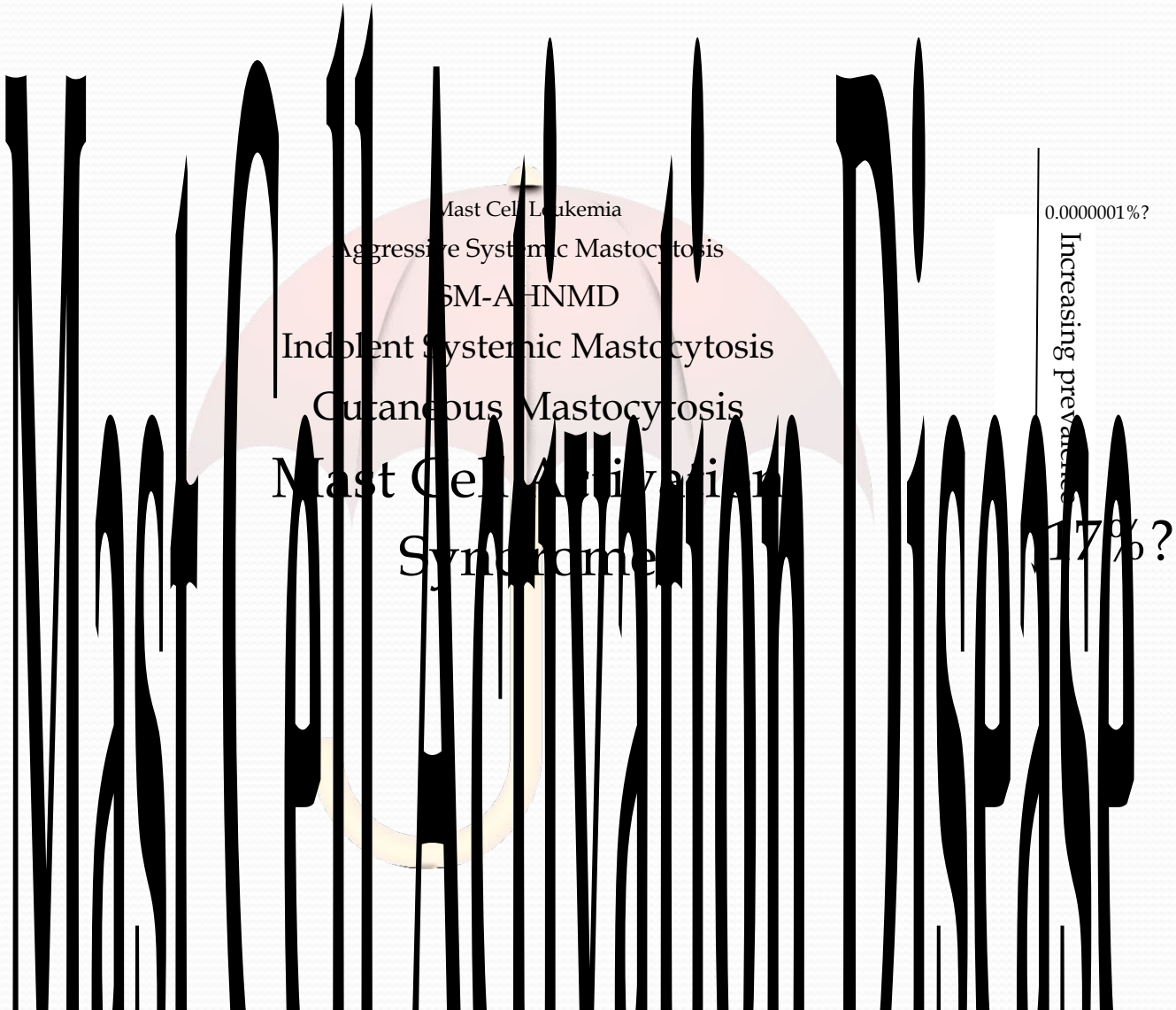
MCAD: A Brief History

Key PubMed IDs

- 1984-91: 1st published hypotheses that MCAS ought to exist
- 2007: 1st case reports of MCAS
  - Some with KIT-D816V, some without
- 2007: 1st study showing other KIT mutations in most MCAS (Bonn) 17710669
- 2008-: Non-KIT mast cell regulatory gene mutations found in SM
- 2010: 2nd study showing KIT mutations in most MCAS (Bonn) 20838788
  - KIT-D816V rare
  - Few mutations in controls
- 2010: Proposal of "MCAD" (Harvard, Vienna, NIH) 20838788
  - Includes 1st proposal for MCAS diagnostic criteria
- 2011: Alternative proposal for MCAS diagnostic criteria (Bonn, MUSC) 21418662
  - Revised 2016, 2017
- 2012: Revised (Vienna et al.) proposal for MCAS diagnostic criteria 2012: 22041891
  - Still problematic
  - "Updated" again in 2019 (now a.k.a. "consensus-1") – no different than 2012 2019: 30737190
- 2016: Revised WHO diagnostic criteria for SM 27069254
  - Mastocytosis now separate from the myeloproliferative neoplasms (MPNs)
  - "Smoldering SM" added; "SM-AHNMD" shortened to "SM-AHN"
  - No statement regarding MCAS
- 2020: "Consensus-2" proposal (update of alternative 2011/2016/2017 proposals) for MCAS diagnostic criteria 32324159

MCAD: Emerging Understanding




Mast Cell Leukemia
Aggressive Systemic Mastocytosis
SM-AHNMD
Indolent Systemic Mastocytosis
Cutaneous Mastocytosis
Mast Cell Activation
Syndrome
0.0000001%?
Increasing prevalence
17%?

Normal mast cell biology

- Hematopoietic origin, brief circulation
  - Normally 0.05% of marrow nucleated cells
  - Typically < 2% even in systemic mastocytosis
  - Unique flow cytometric signature (incl. CD117+, CD25/2-)
- Maturation completed in all vascularized tissues
  - Especially abundant beneath environmentally exposed mucosal/epithelial surfaces and adjacent to blood and lymphatic vessels and nerves, permitting sentinel function
- Relatively immobile once localized in peripheral tissue
- Lifespan typically several months to a few years

Kalesnikoff J, Galli SJ. New developments in mast cell biology. *Nature Immunology* 2008;9:1215-23.
Ribatti D. The development of human mast cells: an historical reappraisal. *Exp Cell Res* 2016;342(2):210-5.

Normal mast cell biology

- Functions (when appropriately stimulated):
  - Synthesize active substances
    - Some stored in granules of highly heterogeneous content
  - Release various mediators upon various triggerings
  - Phagocytose particulate material including bacteria, erythrocytes, schistosomes, metals, etc.
- KIT stem cell factor receptor and tyrosine kinase (on 4q11-12) is expressed at high levels on the mastocyte surface
  - Critical for many mast cell functions including proliferation, differentiation, survival, chemotaxis, adhesion, and activation

Akin C, Metcalfe DD. The biology of mast cells and clinical implications of pharmacogenetics. *J Allergy Clin Immunol* 2004; 114:13–19.
Gordon JR *et al.* Mast cells as a source of multifunctional cytokines. *Immunol Today* 1990;11:458.
Bradding P *et al.* Heterogeneity of human mast cells based on cytokine content. *J Immunol* 1995; 155:297.
Metcalfe DD *et al.* Mechanisms of mast cell signaling in anaphylaxis. *J Allergy Clin Immunol* 2009;124:639-648.

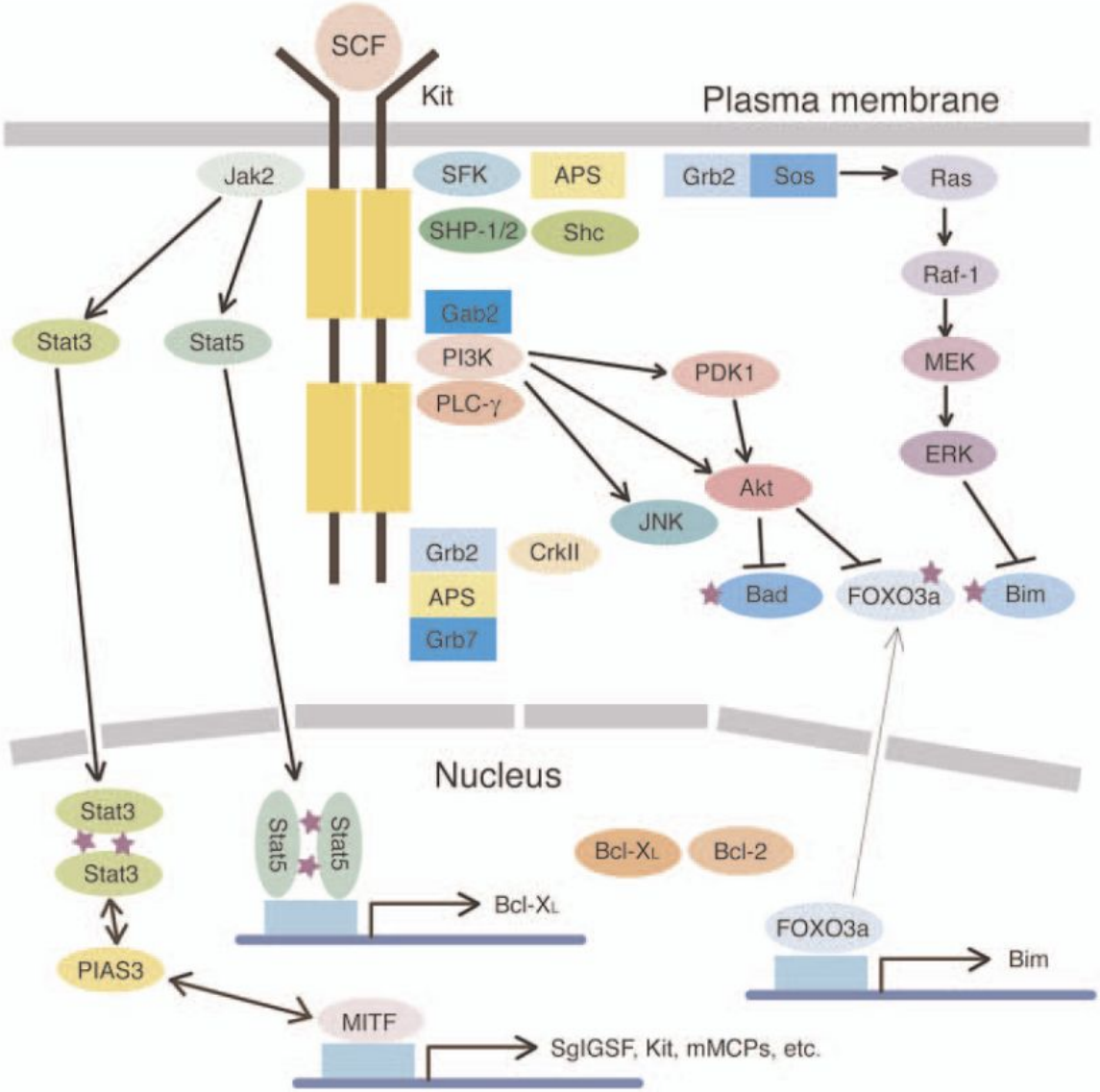
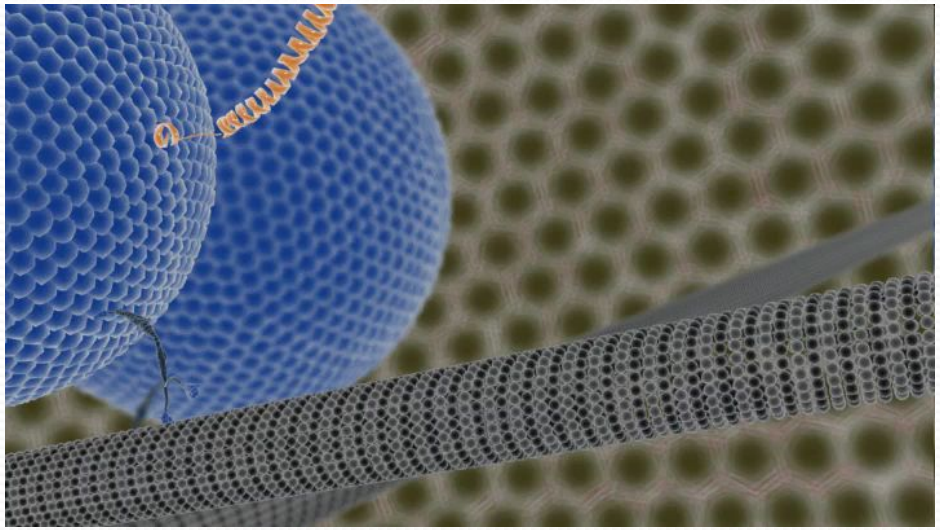


Fig. 2. Kit signaling pathways in mast cells. This figure summarizes signaling proteins activated by Kit. Filled boxes of Kit indicate split kinase domains. Abbreviations: APS, adaptor containing PH and SH2 domains; Grb, growth factor receptor-bound protein; JAK, Janus kinase; JNK, c-Jun NH2-terminal kinase; MEK, mitogen-activated protein kinase kinase; ERK, extracellular regulated protein kinase; MITF, microphthalmia transcription factor; PI3K, phosphatidylinositol 3-kinase; PLCγ, phospholipase Cγ; SCF, stem cell factor; SFK, Src family kinases; Shc, SH2-containing transforming protein C1; SHP, SH2 domain-containing phosphatase; Stat, signal transducers and activators of transcription.

Okayama Y, Kawakami T. Development, migration, and survival of mast cells. *Immunologic Research* 2006;34(2):97-115.

Normal mast cell biology

- Mediator release processes
  - "Traditional": degranulation
    - Fulminant degranulation (e.g., anaphylaxis)
    - Piecemeal (slower) degranulation
  - Transgranulation
  - Secretion of extracellular vesicles



Courtesy of Prof. Peter Smith, Griffith University, Gold Coast, Australia

Vukman KV *et al*. Mast cell secretome: Soluble and vesicular components. *Semin Cell Dev Biol* 2017;67:65-73.
Hügle T. Beyond allergy: the role of mast cells in fibrosis. *Swiss Med Wkly* 2014;144:w13999.

Theoharides TC, *et al. New Engl J Med* 2015;373:163-72, with permission.

Normal mast cell biology

- Capable of synthesizing and releasing many mediators
  - Many expressible at very high levels
  - Some stored in fully active form in electron-dense secretory granules, tightly packaged with serglycin proteoglycans
  - A small sample:

- Pro-inflammatory cytokines
  - IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-15, IL-16, IL-18, IL-21, IL-23, IL-25, IFN-γ, TNF-α
- Chemokines
  - MCP-1, IL-8, RANTES, eotaxin, leukotrienes B_4, C_4, D_4, E_4 (SRS-A), CCL2, CCL3, CCL4, CCL5, CCL11, CCL19, CCL20, CCL21, CXCL8, CXCL10, XCL-1
- Proteases
  - Tryptase, chymase, ACE, carboxypeptidase, cathepsin G, cysteinyl cathepsins, metalloproteinases
- Growth factors
  - IL-3, GM-CSF, bFGF, VEGF, TGF-β, PDGF, EGF, NGF, SCF, angiopoietin
- Vascular permeability, vasodilatation
  - Histamine, 5-hydroxytryptamine, tryptase, NO, VLA4
- Platelet aggregation and thrombosis:
  - PAF, thromboxane
- Heparin proteoglycan
- Chondroitin sulfate proteoglycan
- Superoxide dismutase
- Acid hydrolases
  - Glucuronidase, galactosidase, hexosaminidase, peroxidase
- Arylsulphatase A
- Prostaglandin D_2, thromboxane
- Serotonin
- Antimicrobial agents
  - IFN-α, IFN-β, IFN-γ, cathelicidin, LL-37
- CRH
- TSLP
- Want more? See http://www.cells-talk.com/index.php/page/copelibrary?key=mast%20cells

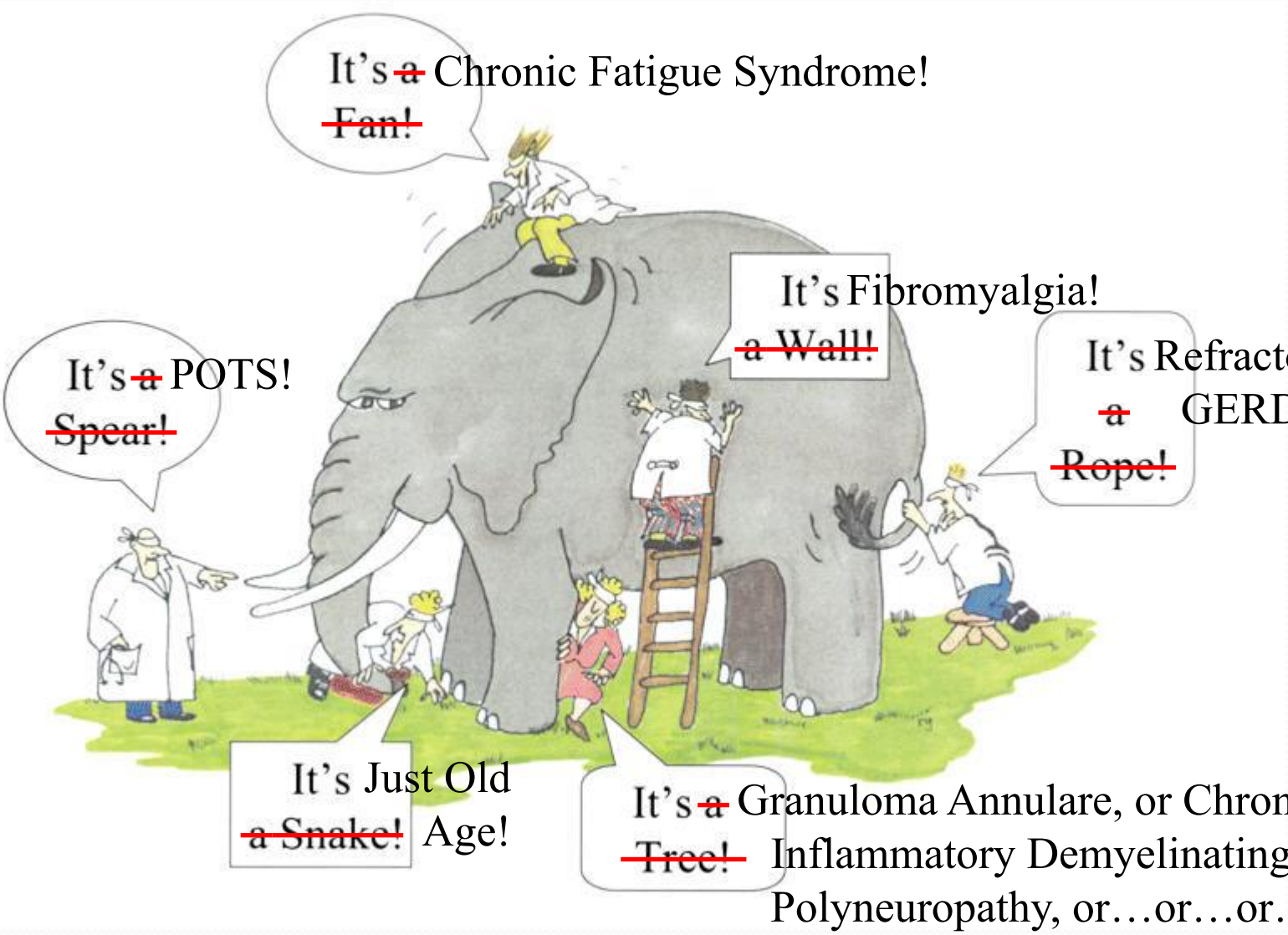
Theoharides TC *et al.* Differential release of mast cell mediators and the pathogenesis of inflammation. *Immunological Reviews* 2007;217(1):65-78.

Criteria for Systemic Mastocytosis

- WHO ’16: Indol. SM, smold. SM, SM-AHN, aggressive SM, MC leukemia
  - 1 major + 1 minor, or 3+ minor criteria
  - Only major criterion: “Multifocal, dense infiltrates of mast cells consisting of 15 or more mast cells in aggregates detected in sections of bone marrow and/or other extracutaneous organs, confirmed by tryptase immunohistochemistry or other special stains”
  - 4 minor criteria:
    - More than 25% of MCs in biopsy sections or bone marrow aspirate smears showing spindle shape or atypical morphology
    - Expression of CD2 and/or CD25 by marrow, blood, or extracutaneous organs MCs
    - KIT codon 816 mutation in bone marrow, blood, or other extracutaneous organs
      - Different KIT mutations → different phenotypes
        - D816V: MC clusters, spindle forms, expression of CD25, histamine, CPA, etc.
        - Extracellular domain: AKT activation
    - Serum total tryptase (25% of MC protein!) persistently > 20 ng/ml

Arber DA et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391-2405.
Mayerhofer M *et al.* Unique effects of KIT D816V in BaF3 cells: induction of cluster formation, histamine synthesis, and early mast cell differentiation antigens. *J Immunol* 2008;180:5466-5476.
Teodosio C *et al.* Mast cells from different molecular and prognostic subtypes of systemic mastocytosis display distinct immunophenotypes. *J Allergy Clin Immunol* 2010;125:719-726.e4.
Yang Y *et al.* Pediatric mastocytosis-associated KIT extracellular domain mutations exhibit different functional and signaling properties... *Blood* 2010 Aug 19, 116(7):1114-1123.
Alvarez-Twose I *et al.* Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *J Allergy Clin Immunol* 2010;125:1269-1278.e2.
Schwartz LB *et al.* Quantitation of histamine, tryptase, and chymase in dispersed human T and TC mast cells. *J Immunol* 1987;138(8):2611-2615.

The Problem


It's ~~a~~ Chronic Fatigue Syndrome!
~~Fan!~~
It's Fibromyalgia!
~~a Wall!~~
It's ~~a~~ POTS!
~~Spear!~~
It's Refractory GERD!
~~a~~
~~Rope!~~
It's Just Old Age!
~~a Snake!~~
It's ~~a~~ Granuloma Annulare, or Chronic Inflammatory Demyelinating Polyneuropathy, or…or…or…!
~~Tree!~~

What to do when it behaves like mast cell disease but isn't just allergic disease or mastocytosis: Consider mast cell activation syndrome

Proposed Criteria for MCAS

- Self-described "consensus" proposal (now a.k.a. "consensus-1")
  - Problem: Methods by which "consensus" was obtained
  - History consistent with chronic and/or recurrent aberrant mast cell mediator release
    - Problem: Few symptoms listed in proposal (e.g., flushing)
  - Not SM and no better-fitting disease
  - Rise in tryptase (within 4h of flare) of 20% + 2 ng/ml over asymptomatic baseline
    - Problem: establishing "asymptomatic" baseline
    - Problem: getting blood for tryptase level drawn within 4h of flare
    - Problem: allows levels well within normal range to signify disease
    - Problem: no published data whether this distinguishes nl./abnl. fluctuation in the general MCAS population despite repeated assertions otherwise
  - Response to mast cell-targeted therapy
    - Problem: requires therapy prior to diagnosis
    - Problem: should diagnosis of this very heterogeneous disease be ruled out if 1 or 2 lines of empiric therapy fail?

Valent P *et al.* Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012 Jan;157:215-225.
Akin C *et al.* Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 2010; 126:1099-1104.e4.
Valent P *et al.* Why the 20% + 2 tryptase formula is a diagnostic gold standard for severe mast cell activation and mast cell activation syndrome. *Int Arch Allergy Immunol* 2019;180(1):44-51, doi: 10.1159/000501079.

Diagnosing MCAS: Criteria

- "Consensus-2" proposal:
  - Major criterion:
    - New ✓ Constellation of clinical complaints attributable to pathologically increased MC activity (MC mediator release syndrome)
  - Minor criteria:
    - Expanded Multifocal or disseminated infiltrates of MCs in marrow and/or extracutaneous organ(s) (e.g., gastrointestinal or genitourinary tract; ≥20 MCs/high power field)
    - Same as WHO Abnormal spindle-shaped morphology in >25% of MCs in marrow or other extracutaneous organ(s)
    - Same as WHO Abnormal MC expression of CD2 and/or CD25 (i.e., co-expression of CD117/CD25 or CD117/CD2)
    - Expanded MC genetic changes (e.g., activating KIT codon 419, 509, or 560 mutations) shown to increase MC activity
    - Expanded ✓ Evidence (typically from body fluids such as whole blood, serum, plasma, or urine) of above-normal levels of MC mediators including: tryptase, histamine or its metabolites (e.g., *N*-methylhistamine), heparin, chromogranin A (note potential confounders of cardiac/renal/hepatic failure, neuroendocrine tumors, chronic atrophic gastritis, or recent proton pump inhibitor use), other relatively MC-specific mediators (e.g., eicosanoids including prostaglandin (PG) D_2, its metabolite 11-β-$PGF_{2\alpha}$, or leukotriene E4)
    - Added Symptomatic response to inhibitors of MC activation or MC mediator production or action
  - Diagnosis made upon fulfillment of the major criterion + ≥ 1 minor criterion…
    - …and, of course, no other evident diagnosis which better accounts for the full range and duration of all the symptoms and findings in the history, exam, and labs

Afrin LB et al., Diagnosis 2020 Apr 22;8(2):137-152. doi: 10.1515/dx-2020-0005, updated from Molderings GJ *et al. F1000Res* 2017 Oct 26;6:1889. doi: 10.12688/f1000research.12730.1, updated from Afrin LB, *et al. Ann Med* 2016;48(3):190-201, updated from Molderings G, *et al. J Hematol Oncol* 2011;4:10.

MCAS: Emerging Understanding

- Increasing estimates of prevalence
  - 1-17% of the general first-world population?

If MCAS dominantly manifests as chronic inflammatory disease (CID), might its prevalence be even higher within populations enriched for CID (e.g., inpatients)?
What Portions of These Populations Bear Clonal Mast Cell Disease?

Theoha
Afrin L
Haenis
Pejler G
Theoha
Theoharides TC, *et al. Trends Pharmacol Sci* 2011;32(9):534-542.
Afrin LB, et al. *Int J Infect Dis* 2020;100:327-332.
Frieling T, *et al., Z Gastroenterol* 2011;49:191-194.
Weinstock LB, et al. *Int J Infect Dis* 2021;112:217-226.

MCAS: Emerging Biology

- May be clonal in most cases…
  - More than 50 mutations (mostly heterozygous, but still functionally dominant) found scattered across all domains of KIT
  - Most patients have multiple KIT (and other) mutations
  - No commercial assays yet for most of these mutations

Molderings GJ *et al.* Multiple novel alterations in Kit tyrosine kinase in patients with gastrointestinally pronounced systemic mast cell activation disorder. *Scand J Gastroenterol* 2007; 42(9):1045-1053.
Molderings GJ *et al.* Comparative analysis of mutation of tyrosine kinase Kit in mast cells from patients with systemic mast cell activation syndrome and healthy subjects. *Immunogenetics* 2010;62:721-727.

MCAS: Emerging Biology

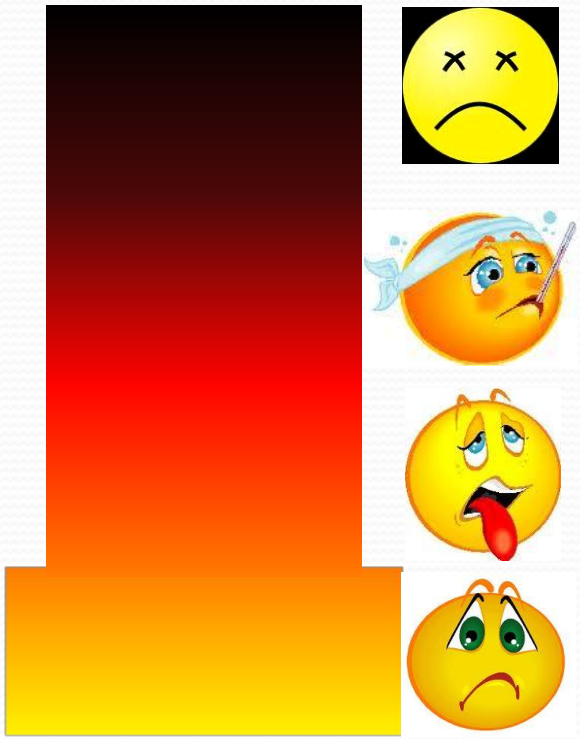
- KIT mutations found thus far in MCAS:
  - Ligand-binding domain: W8R, C12S, del(nt a153), E53K, insertion 71 ?seq(400bp), E73R, T74R, exon 3 & 5 del and ins/del, ins nt 248a, ins Q252, K259E, H265Q, E270K, L276S
  - Dimerization domain: E338K, Q346L, M351E, F355L, E359V, exon 7 ins/del, del (aa 378-390)
  - Proteolytic cleavage site: L416Q, D419H, ins(nt 1282g), exon 8 del
  - Membrane-spanning region: del 510-513, exon 10 ins, M541L
  - Juxtamembrane (autoinhibitory) region: F584C
  - Kinase insert sequence K1: S709A, del(S715), A736V, D751Y
  - Kinase domain K2: F782S, N787D, H790R, D816V (rare!), S821F, A829T, A837V, L862V
  - C-terminus: complex insertions

Molderings GJ *et al.* Multiple novel alterations in Kit tyrosine kinase in patients with gastrointestinally pronounced systemic mast cell activation disorder. *Scand J Gastroenterol* 2007; 42(9):1045-1053.
Molderings GJ *et al.* Comparative analysis of mutation of tyrosine kinase Kit in mast cells from patients with systemic mast cell activation syndrome and healthy subjects. *Immunogenetics* 2010;62:721-727.

MCAS: Do the Biology Math

- MCs produce and release scores of mediators
- 1 KIT mutation ⇒ aberrant release of N mediators
- Multiple KIT mutations in most MCAS patients?
- Multiple MC genes mutated in most MCAS patients?
- Each mediator has its own unique array of direct and indirect, local and remote effects

Potential for Multisystem Polymorbidity and Clinical Heterogeneity

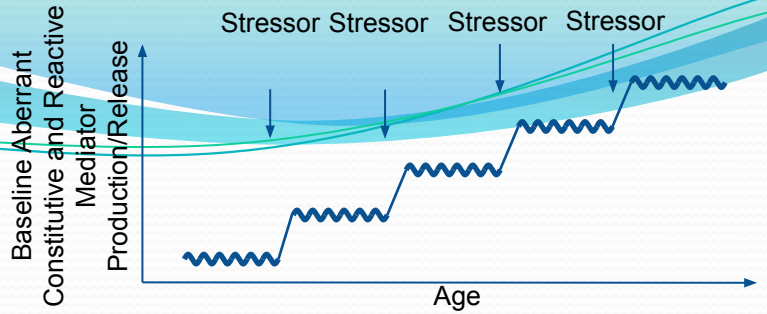


MCAS: Presentation

- MCAS is a chronic multisystem polymorbidity of general themes of:
  - Inflammation – the universal constant in MCAS
  - ± allergic-type phenomena
  - ± aberrancies in growth/development (i.e., dystrophisms), far more commonly benign than malignant in potentially any tissue
    - can be difficult to recognize given typically slow pace of development and, often, lack of clinical significance

Afrin LB, Butterfield JH, Raithel M, Molderings GJ. *Ann Med* 2016;48(3):190-201.

MCAS: Presentation

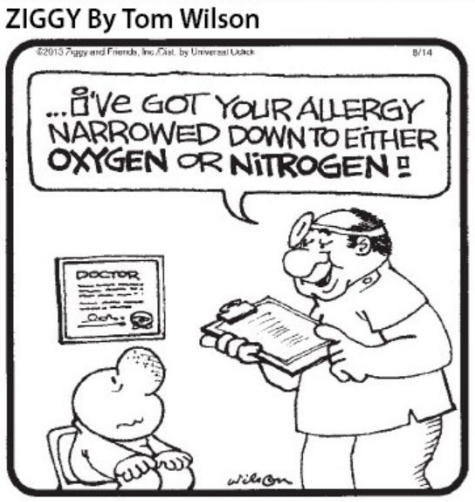


- Typical presentation
  - Age of onset: typically < 20 but unrecognized for decades
    - Escalations of baseline MC misbehavior may shortly follow (by a few days to a few months) major physical or psychological/emotional stressors
  - Usually **MULTISYSTEM**; can affect every system
  - Symptoms virtually always at least "inflammatory" in nature
  - Perplexingly inconstant course:
    - Abnormalities often externally inapparent ("she looks fine!")
    - Chronic or waxing/waning or episodic ("flares", "spells")
    - Different symptoms at different times
    - Often no apparent triggers
  - Mediators:
    - Tryptase (total & mature) usually normal (reflects MC load >> activation)
    - Heparin, CGA, PGD_2 and histamine (& metabolites), LTE4 often elevated
  - Many MDs, many dx's (often non-specific, idiopathic, "somatic")
  - Patients commonly cease reporting symptoms – ROS important!

1. Afrin LB, Butterfield JH, Raithel M, Molderings GJ. *Curr Med Res Opin* 2012;28(3):403-14.
2. Zenker N, Afrin LB. *Blood* 2015;126:5174.
3. Schwartz LB. *J Immunol* 2006;177:5659-67; and *Immunol Allergy Clin North Am* 2006;26:451-63.
4. Hamilton MJ et al. *J Allergy Clin Immunol* 2011;128;147-52.
5. Ferrer M et al. *Clin Exp Allergy* 2010 Dec;40(12):1760-6.
6. Sala-Cunill A et al. *Int Arch Allergy Immunol* 2013;160(2):192-9.

MCAS: Presentation

- Constitutional
  - Fever, chills, fatigue, sweats, weight ↑ or ↓ or ↑↓, pruritus
  - Odd and prolific sensitivities (drugs, foods, environs)
- Eyes
  - Irritation, episodic inability to focus vision, blepharospasm
- Ears
  - Irritation, hearing deficit and/or tinnitus
- Nose
  - Irritation, sores, epistaxis, coryza
- Oral/esophageal
  - Irritation, sores, dysphagia, globus



Afrin LB, Butterfield JH, Martin R, Molderings GJ. *Ann Med* 2016;48(3):190-201.

MCAS: Presentation

- Nodes
  - Borderline pathologic, waxing/waning, migratory adenopathy
  - Left upper quadrant (splenic?) discomfort common
  - Path: usually reactive lymphocytosis, occ. sinus histiocytosis
- Pulmonary
  - Waxing/waning migratory edema/inflammation (e.g., cough)
  - Dyspnea (normal PFTs; “I just can’t catch a deep breath”)
- Cardiovascular
  - Unprovoked presyncope/syncope, labile BP/pulse, palpitations
  - Chest pain: coronaries usually clean, but occ. aggressive CAD
  - Arterial, venous malformations; episodic migratory edema
  - Takotsubo (acute balloon CHF), Kounis (allergic angina) synd.

Afrin LB, Butterfield JH, Martin R, Molderings GJ. *Ann Med* 2016;48(3):190-201.

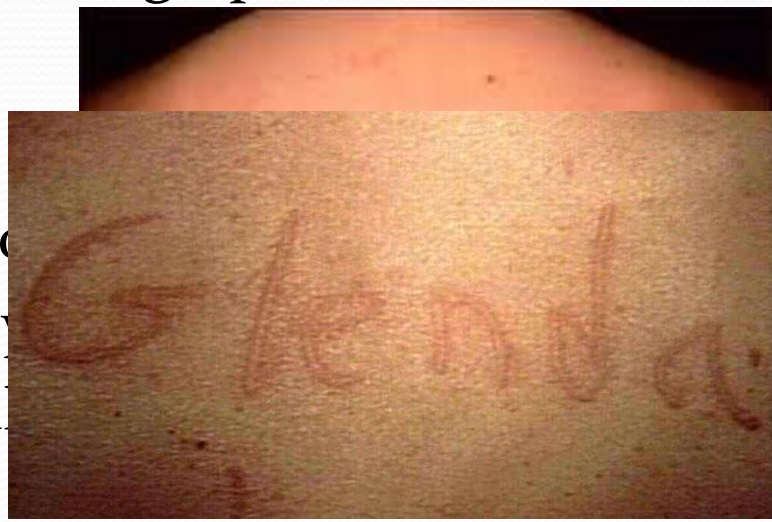
MCAS: Presentation

- GI
  - Inflammation (any/all luminal segments, solid organs)
  - Refractory GERD, IBS, mild ↑LFTs common
  - Diarrhea constipation
  - Queasiness, nausea, vomiting (sometimes "cyclical")
  - Malabsorption common (gen., or selected micronutrients)
  - Hepatic involvement common, usually inflamm./fibrosis
- GU
  - Inflammation (any/all luminal segments, solid organs)
    - e.g., "interstitial cystitis"
  - ↓ libido, infertility

Afrin LB, Butterfield JH, Martin R, Molderings GJ. *Ann Med* 2016;48(3):190-201.

MCAS: Presentation

- Musculoskeletal and Joints
  - Myositis, osteopenia and/or osteosclerosis
  - Diffusely migratory soft tissue pain; “fibromyalgia,” “CRPS”
    - NSAIDs/narcotics often unhelpful (may trigger flares!)
- Skin/Integument
  - Lesions (many types), rashes (many types, often migratory), pruritus, flushing, angioedema, dermatographism
  - Hair/nail/dental dystrophy
- CNS/PNS
  - Headache, vertigo, syncope, tic/treme
  - Migratory paresthesias, insomnia ver
  - Wide range of psychiatric disorders a



Afrin LB, Butterfield JH, Martin R, Molderings GJ. *Ann Med* 2016;48(3):190-201.

MCAS: Presentation

- Heme
  - Counts often normal, or…
    - ↑ or ↓ H/H (subtle ↑ RDW, MCV, and/or MCH common)
    - ↑ or ↓ WBC (subtle/intermit. ↑ monos, eos, &/or basos common)
    - ↑ or ↓ plts
    - ↑ or ↓ clotting
  - Marrow
    - Usually normal (histology, IHC, cytogenetics, flow, PCR)
    - Most common abnormality: mild dysplasia (“unclass. MDS/MPN”)
- Immunity
  - Hypersensitivities, ↑ risk for malig., autoimm., infection
  - Poor healing

Afrin LB, Butterfield JH, Martin R, Molderings GJ. *Ann Med* 2016;48(3):190-201.

MCAS: Presentation

- Endocrinologic/metabolic
  - Delayed puberty/menarche, dysmenorrhea
  - Osteopenia/osteoporosis, osteosclerosis
  - Hypo/hyperthyroidism, hyperferritinemia (inflammatory)
  - ↑ or ↓ electrolytes, ↑ lipids (often hypertriglyceridemia)
- Growth/Development
  - Poor healing
  - Cysts, fibrosis, endometriosis, vascular anomalies, cancer
  - Connective tissue weakness (e.g., hypermobile Ehlers Danlos Syndrome)?
  - Autism spectrum disorders?
  - Inflammatory lipodystrophies (e.g., Dercum's disease)?

Afrin LB, Butterfield JH, Raithel M, Molderings GJ. *Ann Med* 2016;48(3):190-201.
Afrin LB. *Am J Med Genet C Semin Med Genet* 2021 Dec;187(4):466-472.
Herbst, K.L., 2019. *Endotext* [Internet], https://www.ncbi.nlm.nih.gov/sites/books/NBK552156/.

MCAS: Diagnosis

- Best diagnostic aids:
  - Most physicians' best friend: a <u>complete</u> history and exam
  - Faith in Occam's Razor: which scenario is more likely?
    - Multiple diagnoses/problems all independent of each other

MCAS: Diagnosis

- Best diagnostic aids:
  - Most physicians' best friend: a <u>complete</u> history and exam
  - Faith in Occam's Razor: which scenario is more likely?

    - Multiple diagnoses/problems all independent of each other

    vs.

    - One diagnosis that's biologically capable of causing most or all of the findings (i.e., the simplest solution, even if it's not the most immediately obvious solution)

MCAS Differential Diagnosis

- Need to carefully consider the many diseases which drive chronic multisystem inflammatory ± allergic ± dystrophic issues, e.g. (note some of these may, in at least some cases, actually be consequential to MCAS):
  - Autoimmune diseases
  - Adrenal insufficiency
  - Adult Still's disease
  - Cellular and humoral immunodeficiency syndromes
  - Eosinophilic disorders (e.g., eosinophilic esophagitis)
  - Gulf War Illness/Syndrome
  - Inborn metabolic errors
  - Infections (esp. tick-borne/pet-borne diseases)
  - Malignancies (esp. hematologic)
  - Mitochondrial diseases
  - Porphyrias
  - Etc. etc. etc.

MCAS Differential Diagnosis

- Also, in patients with literally life-long multisystem inflammation (i.e., extending back to infancy or early childhood), be sure to test for the **autoinflammatory syndromes** (AISs)
  - Scores of different diseases born of mutations in >150 genes coding proteins regulating various aspects of inflammation
  - An AIS mutation transforms an inflammation-regulating protein that's normally an "on/off switch" into a "switch that's stuck permanently on"
  - Formerly called the periodic fever syndromes – until it became clear fever was not a reliable feature of many of these syndromes
  - Testing previously difficult and expensive, now easy (even internationally) and inexpensive (e.g., Invitae (155 genes), Fulgent (47 genes), Mayo (18 genes), ARUP (10 genes), etc.)
  - **Many AISs** (though not all) **are treatable**
  - Will require testing (not yet clinically available) for somatic mast cell mutations to distinguish whether AIS patients' sole problem is their germline mutation vs. germline + somatic (mast cell) mutations, but either way, decreasing AIS-driven inflammation may (should?) decrease mast cell activation

MCAS Diagnostic Work-Up: 2022

Establish Suspicion:

Signs of mastocytosis (e.g., urticaria pigmentosa, unprovoked flushing or anaphylaxis, wasting, end-organ dysfunction, etc.)?

Symptoms of MC activation (Table 1)? MC mediator release syndrome per validated questionnaire (Figure 4)?

More symptoms/findings than can be explained by definitively established diagnoses? Odd/strange symptoms/findings?

Poor response to treatment of definitively established diagnoses?

↓

Initial Testing:

Biopsy of lesions of suspected cutaneous mastocytosis

Serum tryptase persistently > 20 ng/ml:

- bilateral marrow aspiration/biopsy including MC-specific immunohistochemical staining (e.g., CD117, tryptase, toluidine blue, Giemsa, Alcian blue), multicolor flow cytometry for co-expression of CD117/CD25, CD117/CD2, and molecular testing for KIT mutations as available (PCR for KIT^{D816V} at a minimum)
- biopsy of other extracutaneous tissues (e.g., GI tract) as appropriate, for MC-specific testing as above

Complete blood count (CBC) with manual differential
Common serum chemistries
Quant. Ig profile if frequent infections and/or delayed healing
PT/PTT if easy bruising or bleeding or thromboembolic events

↓

Additional MC Mediator Testing:

Serum chromogranin A (avoid PPIs for 5+ days before testing)
Chilled plasma for PGD_2 (and/or 11-β-$PGF_{2\alpha}$) (avoid NSAIDs for 5+ days before testing)
Chilled plasma histamine
Chilled plasma heparin (if not on exogenous heparin products)
Chilled random and 24-hour urine collections for PGD_2 (and/or 11-β-$PGF_{2\alpha}$) and *N*-methylhistamine
Chilled urine for leukotrienes B4, C4, D4, and E4 (if necessary)

Afrin LB, Molderings GJ. A concise, practical guide to diagnostic assessment for mast cell activation disease. *World J Hematol* 2014 Mar;3(1):1-17.

MCAS: Prognosis

- No epidemiologic studies of prognosis yet
- Present gestalt impression:
  - After the first three years, survival curves parallel the general population (similar to indolent systemic mastocytosis (ISM))
- So, like allergic diseases and ISM, reduced survival is a relatively small problem in MCAS, and instead most suffer reduced quality of life (anywhere from mild to severe, variable over time) until the disease is accurately diagnosed and effectively controlled
- Many therapies (targeting many receptors and pathways) found helpful in various MCAD/MCAS patients
  - Most cytotoxic chemotherapy quite unlikely to help MCAS
- Most MCAS pts eventually identify a significantly helpful regimen…
  - …and given they'll likely live a normal lifespan, the improved quality of life they can achieve – once correctly diagnosed – is important!

Roberts LJ, Anthony LB, Oates JA. "Disorders of Vasodilator Hormones: Carcinoid Syndrome and Mastocytosis" in Wilson JD, Foster DW, Kronenberg HM, *et al., eds., Williams Textbook of Endocrinology, 9th ed.*, 1998, W. B. Saunders Company, Philadelphia, pp. 1718-1732.
Lim K-H, *et al.* Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood* 2009;113:5727-5736.

MCAS: Treatment

- 2022: Largely as for indolent mastocytosis
  - Identify and avoid triggers
  - Inhibit mediator production
  - Inhibit mediator release
  - Block actions of released mediators
  - Cytotoxic and cellular therapy only for aggressive SM, MCL
  - Secondary issues and comorbidities

Again, all treatment options for MCAS discussed in this presentation are ACCME Level Of Evidence “C” as detailed in the Disclaimer slide near the beginning of this presentation.

MCAS: Treatment

- 2021: Largely as for indolent mastocytosis
  - **Identify and avoid triggers, both antigenic (environmental, dietary, medication, etc.) and physical**
    - Or try desensitization therapy if feasible
    - Be aware: medication excipients often are prominent triggers
      - Trying alternative (commercial or compounded) formulations often necessary
    - Low-histamine diets, diamine oxidase supplementation
  - Inhibit mediator production
  - Inhibit mediator release
  - Block actions of released mediators
  - Cytotoxic and cellular therapy only for aggressive SM, MCL
  - Secondary issues and comorbidities

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MCAS: Treatment

- 2021: Largely as for indolent mastocytosis
  - Identify and avoid triggers
  - **Inhibition of mediator production**
    - Steroids (long-term issues), NSAIDs (possibly more likely to be helpful in patients with elevated prostaglandin moieties)
      - Caution re: NSAIDs: some patients react to them; avoid them, or start "low and slow," if concerning history present
    - Vitamin C
    - Possibly also hydroxyurea (or even IMiDs?), TKIs
  - Inhibition of mediator release (stabilization)
  - Blockade of released mediators
  - Rarely (if ever): Cytotoxic therapy
  - Hypothetical: Cellular therapy
  - Secondary issues and comorbidities

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MCAS: Treatment

- 2022: Largely as for indolent mastocytosis
  - Identify and avoid triggers
  - Inhibition of mediator production
  - **Inhibition of mediator release (stabilization)**
    - Cromolyn (oral and/or inhaled – non-absorbed)
      - Can trigger flares 1st few days; tachyphylaxis can abrogate efficacy
    - Pentosan (especially for interstitial cystitis)
    - Tyrosine kinase inhibitors
    - Interferon (& pegylated form?)
    - Omalizumab (anti-IgE)
    - Azathioprine, other immunosupp.
    - JAK1 and mTOR inhibitors?
    - Benzodiazepines and imidazopyridines; cannabinoids; low-dose naltrexone
      - e.g., lorazepam, clonazepam, flunitrazepam, zolpidem; cannabidiol
    - Estrogen receptor modulators? CGRP blockers? TSLP inhibitors? Dupilumab (anti-IL4/IL13)?
  - Blockade of released mediators
  - Rarely (if ever): Cytotoxic therapy
  - Hypothetical: Cellular therapy
  - Secondary issues and comorbidities

Imatinib (approved for CML, ASM, et al.)
Dasatinib (approved for CML, ALL)
Nilotinib (approved for CML)
Sunitinib (approved for renal cell Ca, GIST, pNET)
Midostaurin (approved in AML, ASM/MCL)?
Avapritinib (approved in GIST & ASM)? Masitinib?

Again, all treatment options for MCAS discussed in this presentation are ACCME Level Of Evidence "C" as detailed in the Disclaimer slide near the beginning of this presentation.

Molderings GJ et al. Pharmacological treatment options for mast cell activation disease. *Naunyn Schmiedebergs Arch Pharmacol* 2016 Jul;389(7):671-94.

MCAS: Treatment

- 2022: Largely as for indolent mastocytosis
  - Identify and avoid triggers
  - Inhibition of mediator production
  - Inhibition of mediator release (stabilization)
  - **Blockade of released mediators**
    - Antihistamines (even cont. IV diphenhydramine in severely afflicted pts)
      - Often impressive benefits even absent rhinosinusitis and dyspepsia
      - Can also stabilize mast cells via their autoexcitatory H_1/H_2 receptors
    - Leukotriene antagonists
    - Calcium/vit. D, bisphosphonates, denosumab for osteoporosis/osteopenia
    - TNF antagonists (etanercept, adalimumab, infliximab)?
    - IL-1 antagonists (e.g., anakinra), IL-1β antagonists (e.g., canakinumab)?
    - In development: inhibitors of tryptase, chymase, H_3 receptors, etc. etc.
  - Rarely (if ever): Cytotoxic therapy
  - Hypothetical: Cellular therapy
  - Secondary issues and comorbidities

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MCAS: Treatment

- 2022: Largely as for indolent mastocytosis
  - Identify and avoid triggers
  - Inhibition of mediator production
  - Inhibition of mediator release (stabilization)
  - Blockade of released mediators
  - **Rarely (if ever): Cytotoxic therapy**
    - Hydroxyurea (may work well for bone pain, as in sickle cell disease), alkylators, taxanes, etc.
    - Fludarabine, cladribine, cytarabine, etc.
    - Alemtuzumab, daclizumab
  - Hypothetical: Cellular therapy
  - Secondary issues and comorbidities

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MCAS: Treatment

- 2022: Largely as for indolent mastocytosis
  - Identify and avoid triggers
  - Inhibition of mediator production
  - Inhibition of mediator release (stabilization)
  - Blockade of released mediators
  - Rarely (if ever): Cytotoxic therapy
  - **Hypothetical: Cellular therapy**
    - Allogeneic stem cell transplantation
      - Likely to be extremely challenging
  - Secondary issues and comorbidities

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MCAS: Treatment

- 2022: Largely as for indolent mastocytosis
  - Inhibition of mediator production
  - Inhibition of mediator release (stabilization)
  - Blockade of released mediators
  - Rarely (if ever): Cytotoxic therapy
  - Hypothetical: Cellular therapy
  - **Treatment of secondary issues and comorbidities**
    - Frequent mistake by patients and providers: *Assuming* a symptom (new or old, chronic or acute) is directly due to MCAS
      - MCAS does not render one immune to developing other disease
      - Regardless of the likelihood that a symptom may *ultimately* stem from MCAS, rule out other reasonable diagnostic considerations before assuming MCAS is the (direct) cause!
    - Illnesses secondary to mast cell disease require full treatment until the mast cell disease is controlled, and even then…
    - "…the horse is sometimes already out of the barn": malignancy and autoimmunity rarely, if ever, spontaneously remit simply with control of the underlying mast cell disease

Again, all treatment options for MCAS discussed in this presentation are ACCME Level Of Evidence "C" as detailed in the Disclaimer slide near the beginning of this presentation.

MCAS: Treatment

- Note there are "complementary" treatments, too, in these various therapeutic categories. For example:
  - Inhibition of mediator production and/or release
    - Vitamin C (note kidney stone patients may want to avoid this)
    - Vitamin D
    - Alpha lipoic acid
    - N-acetylcysteine
    - Palmitoylethanolamide (PEA)
    - Cannabidiol (CBD)

1. Hagel AF et al. *Naunyn Schmiedebergs Arch Pharmacol* 2013 Sep;386(9):789-93.
2. Molderings GJ et al. *Naunyn Schmiedebergs Arch Pharmacol* 2016 Jul;389(7):671-94.

Again, all treatment options for MCAS discussed in this presentation are ACCME Level Of Evidence "C" as detailed in the Disclaimer slide near the beginning of this presentation.

MCAS: Treatment

- Many "natural herbs and supplements," too, have anti-inflammatory activity and have potential to help control MCAS via COX-1/-2, MAPK, NFkB, and other pathways, e.g.:
  - Flavonoids (e.g., quercetin, luteolin, ruten)
  - Stilbenoids (e.g., resvera-trol)
  - Alkaloids (e.g., berberine)
  - Lion's mane
  - Elderberry
  - Omega-3 essential fatty acids
  - White willow bark
  - Turmeric/curcumin
  - Green tea
  - Pycnogenol
  - Boswellia
  - Cat's claw
  - Capsaicin
  - Ginseng

Again, all treatment options for MCAS discussed in this presentation are ACCME Level Of Evidence "C" as detailed in the Disclaimer slide near the beginning of this presentation.

1. Maroon JC et al. *Surg Neurol Int* 2010;1:80.
2. Attiq A et al. *Front Pharmacol* 2018 Sep 7; 9:976. doi: 10.3389/fphar.2018.00976.

Again, all treatment options for MCAS discussed in this presentation are ACCME Level Of Evidence "C" as detailed in the Disclaimer slide near the beginning of this presentation.

MCAS: Treatment

- Non-pharmacologic therapies occasionally can be helpful, too
  - For example, certain behavioral re-training programs
  - Typically require longer periods (3-6 months) to see improvement than required by most pharmacological interventions
  - Mechanisms unclear, but seem likely related to the known close interactions – even physical abutment! – of neurons and mast cells throughout the body, with constant mediator "cross-talk" between such dyads

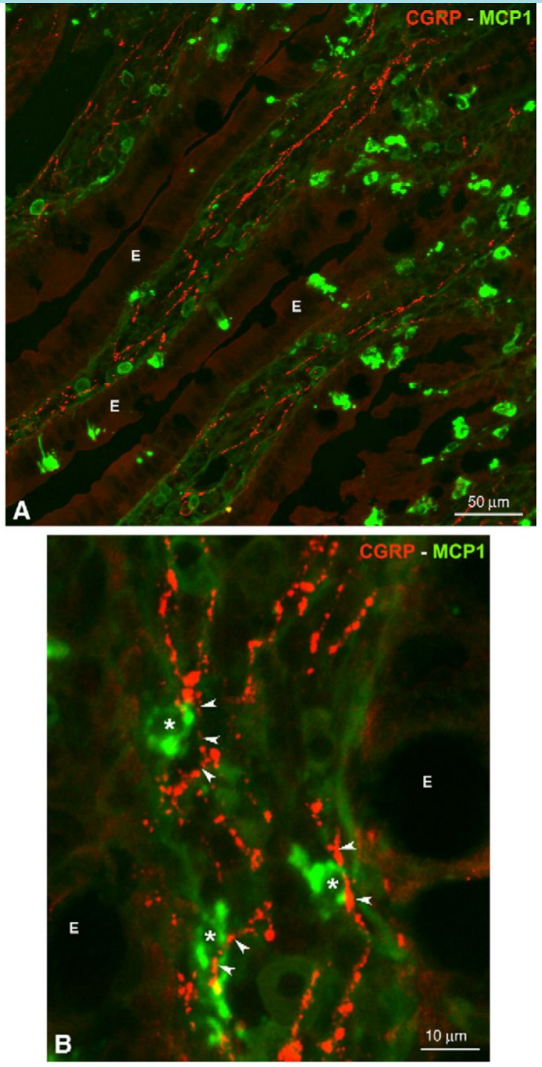

Fig. 1. Low (A) and high (B) magnification of a cryosection double stained for CGRP (red) and mouse mast cell protease 1 (green) of the mucosal layer in the small intestine of a *Schistosoma mansoni*-infected adult mouse, 8 weeks postinfection. Note the close apposition between the afferent CGRP-ir nerve fibres (arrows) and the mucosal mast cells (asterisks). Both nerve sprouting and strong mastocytosis are typical features during the acute and chronic infection stage in this inflammatory model. E: epithelium.

Shown with permission from ref. 6 below.

1. Blennerhassett MG et al. *Cell Tissue Res* 1991 Jul;265(1):121-8.
2. Theoharides TC et al. *Trends Pharmacol Sci* 2004 Nov;25(11):563-8.
3. Theoharides TC. *Life Sci* 1990;46(9):607-17.
4. Barbara G et al. *Gastroenterology* 2007 Jan;132(1):26-37.
5. Newson B et al. *Neuroscience* 1983 Oct;10(2):565-7,569-70.
6. Van Nassauw L et al. *Autonom Neurosci* 2007 Apr 30;133(1):91-103.

MCAS: Key Nursing Care Issues

- Patient-Professional Trust Issues
  - An MCAS patient's distrust of health care professionals (MDs, RNs, etc.) is born out of years of:
    - Professionals not listening to patient's complaints
    - Professionals denying/dismissing/mocking patient's complaints
    - Misdiagnoses of psychosomatism & Munchausen's (& by proxy) despite careful case review showing such just isn't possible
      - Note neuropsychiatric issues (most common psych issues: anxiety, depression) are COMMON in MCAS but almost always are SECONDARY to the MCAS
    - Repeated failure to think of, and establish, convincing/unifying diagnoses
    - Repeated failure to find significant/explanatory abnormalities in tests
    - Repeated failure of empirically tried treatments to provide significant benefit
    - Repeated failure to identify sensible directions for further

MCAS: Key Nursing Care Issues

- MCAS patients often have remarkable sensitivities/ reactivities to:
  - Substances
    - Foods
    - Odors/fragrances
      - MCAS patients CAN smell, and react to, food odors in the nurses' lounge at the opposite end of the ward
    - Chemicals (detergents, soaps, petroleum-based products…), whether natural or artificial, whether liquid or solid or aerosolized
    - Environmental exposures: pollens, molds, animal danders, etc.
    - Medication products (ESPECIALLY EXCIPIENT INGREDIENTS!)
      - When an MCAS patient tells you he/she can only tolerate certain formulations of a drug, he/she is not kidding!
        - Intolerable formulation = risk for anaphylaxis or other serious rxns
      - These are the patients with the "impossible" reactivities, i.e., reactivities to medications "everybody" tolerates, reactivities to "inert" implanted materials, *apparent* reactivities to saline

MCAS: Key Nursing Care Issues

- MCAS patients often have remarkable sensitivities/ reactivities to:
  - Activities
    - MCAS is highly associated with chronic fatigue syndrome (CFS)
      - Poor stamina, unusual post-exertional fatigue
    - MCAS is highly associated with postural orthostatic tachycardia syndrome (POTS)
      - Poor tolerance of orthostatic changes
      - Significant lability of BP and/or pulse is COMMON
    - MCAS is highly associated with hypermobile Ehlers Danlos Syndrome (hEDS)
      - Diffuse pain; sometimes trivially easy joint dislocations
    - MCAS patients often easily bruise/bleed from trivial triggers
      - Aberrant heparin release by dysfunctional mast cells in a particular site + very short half-life of heparin at body temperature = significant LOCAL bleeding with no detectable significant SYSTEMIC coagulopathy

MCAS: Key Nursing Care Issues

- MCAS patients often have remarkable sensitivities/ reactivities to:
  - Physical forces
    - Changes in TEMPERATURE (note, too, their frequent dysautonomias include frequent poor temp./sweat regulation)
    - Changes in PRESSURE (sometimes as subtle as changes in air pressure, such as with an approaching storm)
    - Loud noises (misophonia)
    - Low wavelengths (bass tones, vibrations)
    - High wavelengths (high audio tones, ultraviolet (e.g., from not only sun but also fluorescent lights!), radio (WiFi!), gamma (radiotherapy))
    - Electric shocks (static electricity exposures)
      - Curiously, ECT usually is well tolerated, possibly due to mast-cell-stabilizing pre-medications

Characterization of MCAS

TABLE 1. Most common (frequency ≥ 10%) comorbidities in mast cell activation syndrome (MCAS). The denominator for each frequency is the eligible portion of the study population (e.g., osteoarthritis: all patients [*N* = 413]; miscarriage: only females [*N* = 287]).

Comorbidity	Frequency (%)	Comorbidity	Frequency (%)
Gastroesophageal reflux disease	35	Sleep apnea	15
Hypertension	29	Freq. upper resp. infections	15
Multiple/atypical drug reactions	23	Miscarriage	15
Abdominal pain NOS	22	Pharyngitis or tonsillitis or both	14
Hysterectomy/oophorectomy	21	Dysmenorrhea	14
Hyperlipidemia	20	Thromboembolism	13
Cholecystectomy	20	Freq. or atypical infections or both	13
Environmental allergies	19	Obesity	13
Tobacco abuse	18	Osteoarthritis	13
Asthma	18	Anxiety or panic or both	12
Diabetes mellitus type 2	17	Vertebral disease	12
Hypothyroidism	17	Cardiovascular malformations	12
Headaches	17	Dermatitides	11
Depression	16	Presyncope or syncope or both	11
Sinusitis	16	Interstitial cystitis	11
Fibromyalgia	16	Chronic kidney disease	10
Anemia of chronic inflammation	15	POTS	10

NOS, not otherwise specified; POTS, postural orthostatic tachycardia syndrome.

Afrin LB, Self S, Menk J, Lazarchick J. *Am J Med Sci* 2017;353(3):207-215.

Characterization of MCAS

TABLE 2. Most common (frequency ≥ 10%) symptoms in mast cell activation syndrome (MCAS). The denominator for each frequency is the eligible portion of the study population (e.g., fatigue: all patients [*N*= 413]; dysmenorrhea: only females [*N* = 287]).

Symptom	Frequency (%)	Symptom	Frequency (%)	Symptom	Frequency (%)
Fatigue	83	Palpitations/dysrhythmias	47	Poor healing	23
Fibromyalgia-type pain	75	Sweats	47	Sinusitis	17
Presyncope/syncope	71	Environmental allergies	40	Weight gain/obesity	17
Headache	63	Fever	40	Dental deterioration	17
Pruritus/urticaria	63	Nonanginal chest pain	40	Weight loss	16
Paresthesias	58	Easy bleeding/bruising	39	Cough	16
Nausea and vomiting	57	Alternating diarrhea/ constipation	36	Anxiety/panic	16
Chills	56	Proximal dysphagia	35	Multiple/odd drug reactions	16
Migratory edema	56	Insomnia	35	Dysmenorrhea	16
Eye irritation	53	Flushing ± diaphoresis	31	Asthma	15
Dyspnea	53	Visual anomalies	30	Alopecia	15
Gastroesophageal reflux	50	Oral irritation/sores	30	Constipation	14
Cognitive dysfunction	49	Adenopathy/adenitis	28	Depression	13
Rashes	49	Diarrhea	27	Tremor	13
Abdominal pain	48	Urinary sympt. excluding IC	27	Onychodystrophy	13
Throat irritation	48	Frequent or odd infections	27	Heat or cold intolerance or both	13

IC, interstitial cystitis.

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Characterization of MCAS

TABLE 3. Most common (frequency $\geq$ 10%) physical examination findings in mast cell activation syndrome (MCAS). The denominator for each frequency is the entire study population ($N = 413$).

Examination finding	Frequency (%)	Examination finding	Frequency (%)	Examination finding	Frequency (%)
Dermatographism	76	Achy appearance	28	Pallor	13
Tired appearance	47	Bruising	22	Moderate systolic hypertension (160-179 mm Hg)	12
Chronically ill appearance	42	Deterioration of dentition (any type, any extent)	21	Use of devices to assist mobility	12
Edema (any degree)	39	Paresthesia	20	Cognitive dysfunction ("brain fog")	12
Obesity (any degree)	37	Epigastric tenderness	19	Flushing	12
Edema (trace)	35	LUQ abdominal tenderness	19	Weakness (global or focal)	12
Rash (any type)	34	Edema (more than trace)	16	Back tenderness (one or more points)	11
Mild systolic hypertension (140-159 mm Hg)	32	Soft tissue tenderness	16	Anxiety	11
Abdominal pain (any location, any type and any severity)	32	RUQ abdominal tenderness	15	Depressed affect	11
Tachycardia	28	Mild diastolic hypertension (90-109 mm Hg)	14	Cardiac murmur	11

LUQ, left upper quadrant; RUQ, right upper quadrant.

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Characterization of MCAS

TABLE 4. Most common medical problems in the families of patients with mast cell activation syndrome (MCAS), extending up to 2 generations backward and 1 generation forward and including first- and second-degree relatives. Only problems occurring in the families of at least 5% of the patients in this study are shown here; the full listing of medical problems found in the families of this study's patients is shown in Online Supplementary Table S4.

Family medical problem	Frequency (%)	Family medical problem	Frequency (%)
Breast cancer	26	TIA/CVA	8
Atherosclerosis	21	Cancer NOS	8
Diabetes mellitus type 2	19	Asthma	7
Lung cancer	18	Environmental allergies	7
Hypertension	17	Leukemia/MDS	7
Osteoarthritis	16	Sickle disease	5
Rheumatoid arthritis	15	Head and neck cancer	5
Colon cancer	15	Non-Hodgkin's lymphoma	5
Prostate cancer	10	Brain cancer	5
Lupus	10		

CVA, cerebrovascular accident; MDS, myelodysplastic syndrome; NOS, not otherwise specified; TIA, transient ischemic accident.

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Characterization of MCAS

TABLE 5. Common abnormalities in routine hematologic and serum chemistry tests found in the study population. The denominator for each frequency is the full cohort of 413 patients.

Hematologic abnormality	Percent	Hematologic abnormality	Percent
RBCs: anemia (RBC, Hgb or Hct < LLN)	66%	WBCs: leukopenia	37%
RBCs: JAK2-w.t. polycythemia (RBC, Hgb or Hct > ULN)	8%	WBCs: leukocytosis	45%
RBCs: microcytosis	24%	WBCs: monocytosis (relative or absolute)	44%
RBCs: macrocytosis	29%	WBCs: eosinophilia (relative or absolute)	40%
RBCs: ↑ mean corpuscular hemoglobin	47%	WBCs: basophilia (relative or absolute)	25%
RBCs: ↑ mean corpuscular hemoglobin concentration	41%	WBCs: reactive lymphocytosis	25%
Platelets: thrombocytopenia	25%	Platelets: thrombocytosis	25%
Chemistry abnormality	**Percent**	**Chemistry abnormality**	**Percent**
↑ Glucose	75%	↑ ALT	38%
↑ Chloride	50%	↓ Sodium	35%
↓ Albumin	44%	↑ Alkaline phosphatase	34%
↓ Potassium	41%	↑ Creatinine	33%
↑ AST	40%		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hct, hematocrit; Hgb, hemoglobin; LLN, lower limit of normal; Pct, percentage of the study population showing the indicated abnormality at least once before MCAS diagnosis; RBC, red blood cell count; RBCs, red blood cells; ULN, upper limit of normal; WBCs, white blood cells; w.t., wild type.

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Characterization of MCAS

TABLE 6. Relative utilities of assorted mast cell mediators in diagnosing mast cell activation syndrome (MCAS). As multiple assays, with different normal ranges, were used for each test across the study population (and even within a given patient's medical record over time), all values are calculated from normalized test results, assuming each assay's reference range encompassed 2 standard deviations greater than and less than the range's midpoint; as such, a value < -2 is less than the parameter's lower limit of normal, > 2 is greater than the upper limit of normal, and a value between -2 and 2 is normal.

Mediator	Minimum normal value	Maximum normal value	Mean normal value	Median normal value	Percent of ↑ tests	Percent of ↑ pts.	Characterization of elevated results (normalized values)			
							Minimum	Maximum	Mean	Median
sTryp	−1.50	67.56	0.81	0.02	15%	16%	2.04	67.56	5.77	3.45
sCgA	−1.60	687.36	19.68	1.74	48%	49%	2.04	687.36	41.07	8.07
$pPGD_2$	−2.90	27.40	2.27	1.20	40%	46%	2.05	27.40	5.60	4.05
pHist	−1.78	64.00	2.81	2.00	41%	49%	2.50	64.00	6.05	4.00
pHep	−2.00	32.00	4.66	2.00	45%	48%	4.00	32.00	12.16	12.00
$24uPGD_2$	−3.76	195.07	2.75	1.27	41%	44%	2.02	195.07	7.43	4.78
24uNMH	−2.35	49.93	0.45	−0.02	10%	11%	2.12	49.93	5.77	2.71
$ruPGD_2$	−4.00	36.87	0.65	0.36	22%	26%	2.02	36.87	8.32	5.41
ruNMH	−2.26	6.68	−0.06	−0.28	5%	7%	2.02	6.68	3.28	2.64

Percent of ↑ pts., percentage of the study population which underwent at least one test for the indicated parameter and which showed at least one elevated result for that parameter; Percent of ↑ tests, percentage of testings of the indicated parameter which showed an elevated result; pHep, plasma heparin; pHist, plasma histamine; ruNMH, random urinary N-methylhistamine; $ruPGD_2$, random urinary prostaglandin D_2; sCgA, serum chromogranin A; sTryp, serum tryptase; 24uNMH, 24-hour urinary N-methylhistamine; $24uPGD_2$, 24-hour urinary prostaglandin D_2.

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- Adrenal fatigue/insufficiency/deficiency
- Adult Still's disease
- Alagille Syndrome type 2
- Allergic rhinitis
- Alopecia areata
- Alopecia universalis
- Anemia of chronic inflammation
- Ankylosing spondylitis
- Anti-phospholipid antibody syndrome
- Anxiety/panic disorders
- Aplastic anemia
- Asthma
- Atypical angina
- Atypical nephrolithiasis
- Autism spectrum disorders
- Autoimmune polyendocrine syndrome type II
- Behcet's disease
- Bell’s palsy
- Benign ethnic leukopenia
- Benign neoplasia (any type; e.g., lipomas, cysts, etc.)
- Bipolar affective disorder (type 1 or 2)
- Bleomycin-induced pulmonary fibrosis
- Blood pressure lability
- Blurry vision (episodic)
- Budd-Chiari syndrome
- Bullous pemphigoid
- Burning mouth syndrome
- Cannabis hyperemesis syndrome
- Cataplexy
- Celiac disease
- Chilblains
- Cholecystitis
- Cholelithiasis
- Chronic constipation (idiopathic)
- Chronic cough (idiopathic)
- Chronic diarrhea (idiopathic)
- Chronic dyspepsia (idiopathic)
- Chronic fatigue syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Chronic low back/pelvic pain (idiopathic)
- Chronic nausea (idiopathic)
- Chronic rhabdomyolysis
- Collagenous colitis
- Colon cancer
- Congestive heart failure
- Contact dermatitis
- Coronary and peripheral artery disease
- Cranio-cervical instability (CCI)
- Cronkhite Canada syndrome
- Cyclic vomiting syndrome
- Delayed-type hypersensitivity drug reaction
- Depression
- Diabetes insipidus and mellitus (types 1 and 2)
- Difficult/complicated sickle cell anemia
- Diverticulitis
- Dysphoric milk ejection reflex (D-MER)
- Eclampsia
- Eczema
- Endometriosis
- Eosinophilic esophagitis (EoE)
- Eosinophilic colitis/gastroenteritis
- Epiploic appendagitis
- Erectile dysfunction
- Erythema multiforme
- Erythromelalgia
- Essential tremor
- Exploding head syndrome
- Fibromuscular dysplasia (FMD)
- Fibromyalgia
- Fibrous histiocytoma
- Focal segmental glomerulonephritis
- GastroEsophageal Reflux Disease (GERD)
- Gilbert’s syndrome
- Gleich syndrome
- Gout (some forms)
- Granuloma annulare
- Gray platelet syndrome
- “Growing pains”
- Gulf War Illness/Syndrome
- Hajdu-Cheney Syndrome
- Hashimoto's thyroiditis
- Hemorrhagic hidradenitis
- Heparin-induced thrombocytopenia
- Hidradenitis suppurativa
- Histiocytosis X and Erdheim-Chester syndrome
- Hodgkin’s lymphoma
- Hyperemesis gravidarum
- Hypermobile Ehlers Danlos Syndrome (hEDS)
- Hypersensitivity vasculitis
- Hypertension (essential)
- Idiopathic adenopathy
- Idiopathic anaphylaxis
- Idiopathic angioedema
- Idiopathic bradycardia
- Idiopathic conjunctivitis
- Idiopathic delayed puberty
- Idiopathic edema
- Idiopathic elevated erythrocyte sedimentation rate or C-reactive protein
- Idiopathic fibrosis/sclerosis (e.g., mediastinal, retroperitoneal)
- Idiopathic hemochromatosis
- Idiopathic hemorrhagic or embolic stroke or TIA
- Idiopathic hepatitis/transaminitis
- Idiopathic hypercoagulability
- Idiopathic hypereosinophilic syndrome
- Idiopathic hypoglycemia
- Idiopathic hypokalemia
- Idiopathic hypomagnesemia
- Idiopathic hypotension
- Idiopathic hypothyroidism
- Idiopathic immunodeficiency
- Idiopathic nonspecific autoimmunity
- Idiopathic pancreatitis
- Idiopathic paresthesias (periph. neuropathy) (EDN-related?)
- Idiopathic pruritus
- Idiopathic pulmonary fibrosis
- Idiopathic rash
- Idiopathic splenomegaly
- Idiopathic/inappropriate sinus tachycardia
- Idiopathic vasculitis
- Idiopathic weight gain
- Idiopathic weight loss
- Implant-related illness (IRI)
- Infertility
- Inflammatory bowel disease (Crohn and ulcerative colitis)
- Interstitial cystitis
- Irritable/inflammatory bowel syndrome
- Juvenile rheumatoid arthritis
- (Progressive) Kaposi’s sarcoma
- Kidney failure
- Keratosis pilaris
- Kleine-Levin Syndrome
- Lactose/fructose/sucrose intolerance
- Leukocytosis (idiopathic)
- Leukopenia (idiopathic and “benign ethnic”)
- Loin pain hematuria syndrome
- Low libido
- Lupus
- Lymphocytic colitis
- Macrophage activation syndrome/HLH (HPS)
- Malignant neoplasia (any type)
- Median arcuate ligament syndrome
- Mesenteric adenitis
- Micronutrient malabsorption/intolerance
- Microscopic colitis
- Migraine and other idiopathic headaches
- Miscarriage (early or otherwise)
- Misophonia
- Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
- Mixed connective tissue disease
- Monoclonal gammopathy of undetermined significance
- Multiple chemical sensitivity (MCS)/toxicant-induced loss of tolerance (TILT)
- Multiple Evanescent White Dot Syndrome (MEWDS)
- Multiple sclerosis
- Myelofibrosis
- Myasthenia gravis
- Myelodysplastic syndrome (esp. w/ nl. cytogenetics)

- Narcolepsy
- Nephrolithiasis
- Night chills (idiopathic)
- Night sweats (idiopathic)
- Neuromyelitis optica
- Nocturnal leg cramps (idiopathic)
- Non-alcoholic steatotic hepatitis (NASH)
- Non-celiac gluten sensitivity
- Nonspecific arthritis
- Nonspecific myalgias
- Nonspecific vasculitis
- Nutcracker syndrome
- Obesity
- Obsessive-compulsive disorder
- Osteopenia/osteoporosis
- Osteosclerosis
- Panic disorder
- Paroxysmal dystonia or torticollis in infancy
- Paroxysmal exertion-induced dyskinesia
- Paroxysmal hypnogenic dyskinesia
- Paroxysmal kinesigenic dyskinesia
- Paroxysmal non-kinesigenic dyskinesia
- Pelvic congestion syndrome
- Pelvic floor instability
- Pemphigus vulgaris
- Periodic hypokalemia
- Periodic paralysis
- Persistent genital arousal disorder (PGAD)
- Polycystic kidney disease
- Polycystic ovarian syndrome (PCOS)
- Polycythemia (without JAK2 mutation)
- Polymyalgia rheumatica
- Post-coital dysphoria (PCD)
- Post-orgasmic illness syndrome (POIS)
- Post-partum depression/psychosis
- Post-traumatic stress disorder
- Postural orthostatic tachycardia syndrome (POTS)
- Pre-eclampsia
- Premature contractions
- Premenstrual dysphoric disorder
- Premenstrual syndrome
- Prostate cancer
- Pseudoxanthoma elasticum
- Psoriasis
- Red Ear Syndrome
- Refractory dizziness
- Relapsing polychondritis
- Restless genital syndrome
- Restless leg syndrome
- Rheumatoid arthritis
- Sarcoidosis
- Schizophrenia
- Schnitzler syndrome
- Scleroderma
- Senile purpura
- Serpentine fibula-polycystic kidney syndrome
- Severe postprandial fatigue
- Sickle nephropathy
- Sickle pulmonary hypertension
- Sjogren’s disease
- Small fiber neuropathy
- Small intestinal bacterial overgrowth (SIBO)
- Spontaneous human combustion
- Substance abuse
- SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing)
- Tachy-brady syndrome
- TEMPI syndrome
- Temporomandibular joint (TMJ) syndrome
- Thrombocytopenia (idiopathic)
- Thrombocytosis (idiopathic and essential)
- Thyroid dysfunction (hyperthyroidism or hypothyroidism, detectably autoimmune or not)
- Tics (idiopathic)
- Tinnitus (idiopathic)
- Tn polyagglutination syndrome
- Unchelatable sickle transfusional hemosiderosis
- Unspecified connective tissue disease
- Unspecified porphyria
- Unspecified sideroblastic anemia
- Urticaria (all forms)
- Uveitis
- Vascular anomalies (aneurysms, hemangiomas, etc.)
- Vestibular neuritis
- Waldenstrom’s macroglobulinemia
- Wolff-Parkinson-White syndrome

Total: 240

- Placeholder

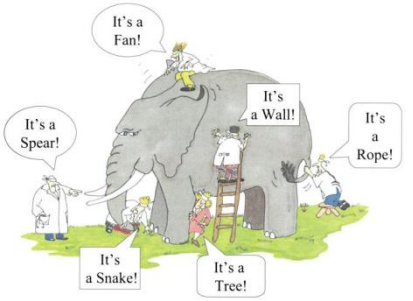
MCAD: Other Research Ideas

- Characterization of Mast Cell Regulatory Gene Mutations in MCAS
- MCAD in Chronic Fatigue Syndrome
- MCAD in Fibromyalgia
- MCAD in Irritable Bowel Syndrome
- MCAD in Refractory GERD
- MCAD in Asthma
- MCAD in Obesity
- MCAD in Hypermobile Ehlers-Danlos Syndrome
- MCAD in Postural Orthostatic Tachycardia Syndrome
- MCAD in Atherosclerotic Vascular Disease
- MCAD in Multiple Chemical Sensitivity (MCS)/Toxicant-Induced Loss of Tolerance (TILT)
- MCAD in Gulf War Illness
- MCAD as a Significant Modifier in Sickle Cell Disease
- Etc. etc. etc. etc.

MCAD: What's next?

- **RESEARCH**
  - Improved diagnostic techniques
    - Early genomic sequencing of isolated mast cells to distinguish primary from secondary disease and identify mutational patterns correlating with various clinical presentations?
  - Etiology
    - Environmental? Genetic? Epigenetic? Viral?
  - Therapy
    - Predictive biomarkers
    - Targeted therapies
- **EDUCATION** (providers, payers, patients, grantors)

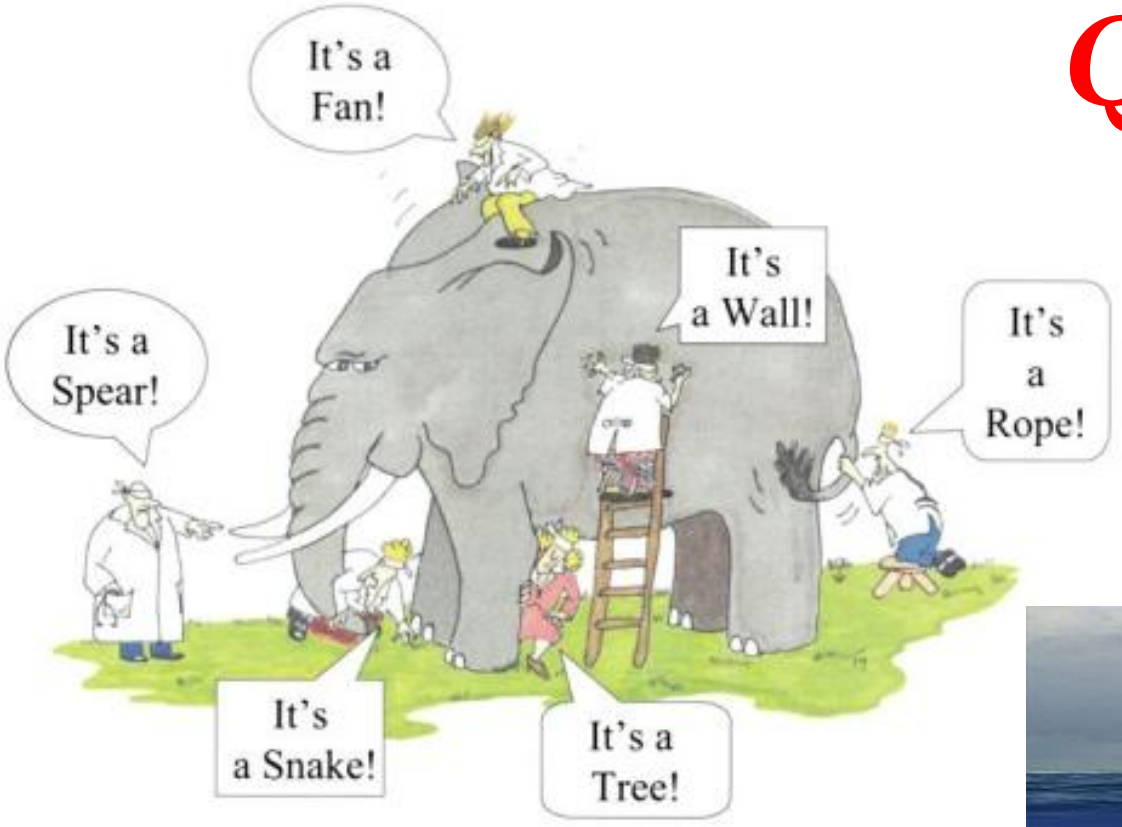
Summary



MCAD Diagnostic Class	General Prevalence	Phenotype	Tryptase usually…
Allergic Diseases	Prevalent	Allergy ± Inflammation	Normal
Mastocytosis	Rare	MC Neoplasia ± Inflamm./Allergy	Elevated
MCAS	Prevalent	Inflamm. ± Allergy ± Dystrophism	Normal

- Tryptase dominantly reflects total body MC load, not activation state
- MCAD symptoms usually from MC activation, not MC load
- Most MCAD patients…
  - …have normal survival, making disease control even more important (QoL!)
  - …can eventually find significantly helpful therapy once diagnosed
- Challenges:
  - Heterogeneity of MCAS (mutational origin?)
  - Many helpful therapies already found, but few biomarkers yet identified which reliably predict helpful therapy; persistence at trial & error needed
  - Education of patients, providers, payers, regulators, grantors, pharma, etc. etc. etc.

Questions?



Questions later?
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