A Collection of publications on the subject of Mast Cell Activation Syndrome
May 2017

Top Ten Papers – Pages 2 - 12

Detailed Bibliography of Other Papers
(with Hypertext links to publications)

Diagnostic Process / General – Page 13
Testing for MCAS – Page 14
Treatment Options – Page 15
Comorbidities – Page 16
Genetics of MCAS – Page 17
TOP 10 MCAS MUST READ PAPERS


**Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options.**


**Author information**
Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN, USA; Program for the Study of Mast Cell and Eosinophil Disorders, Mayo Clinic, Rochester, MN USA; Department of Internal Medicine, Waldkrankenhaus St. Marien, Erlangen, Germany; Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany.

**Abstract**
Mast cell (MC) disease has long been thought to be just the rare disease of mastocytosis (in various forms, principally cutaneous and systemic), with aberrant MC mediator release at symptomatic levels due to neoplastic MC proliferation. Recent discoveries now show a new view is in order, with mastocytosis capping a metaphorical iceberg now called "MC activation disease" (MCAD, i.e. disease principally manifesting inappropriate MC activation), with the bulk of the iceberg being the recently recognized "MC activation syndrome" (MCAS), featuring inappropriate MC activation to symptomatic levels with little to no inappropriate MC proliferation. Given increasing appreciation of a great menagerie of mutations in MC regulatory elements in mastocytosis and MCAS, the great heterogeneity of MCAD’s clinical presentation is unsurprising. Most MCAD patients present with decades of chronic multisystem polymorbidity generally of an inflammatory ± allergic theme. Preliminary epidemiologic investigation suggests MCAD, while often misrecognized, may be substantially prevalent, making it increasingly important that practitioners of all stripes learn how to recognize its more common forms such as MCAS. We review the diagnostically challenging presentation of MCAD (with an emphasis on MCAS) and current thoughts regarding its biology, epidemiology, natural history, diagnostic evaluation, and treatment.

PMID: **27012973** DOI: 10.3109/07853890.2016.1161231
The presentation, diagnosis and treatment of mast cell activation syndrome
Lawrence B Afrin

Author information
Division of Hematology/Oncology, Medical University of South Carolina, Charleston, SC, USA

Abstract
First recognized in 1991 and finally termed such in 2007, “mast cell activation syndrome” (MCAS) is a large, likely quite prevalent collection of illnesses resulting from MCs which have been inappropriately activated but which, in contrast to the rare “mastocytosis,” are not proliferating, or otherwise accumulating, to any significant extent. Due to the marked diversity of direct and indirect, local and remote biological effects caused by the plethora of mediators released by MCs, MCAS typically presents as chronic, persistent or recurrent, waxing and waning or slowly progressive multisystem polymorbidity generally, but not necessarily, of an inflammatory theme. Suspected to be of clonal origin in most cases, MCAS usually is acquired relatively early in life via unknown mechanisms; interaction of environmental factors with inheritable risk factors is one possibility. Initial manifestations often occur in childhood or adolescence but are non-specific; in fact, virtually all of the syndrome’s manifestations are non-specific, leading to decades of mysterious illness (and incorrect diagnoses often poorly responsive to empiric therapies) prior to diagnosis. A large menagerie of mutations in MC regulatory elements has been found in MCAS patients; most patients appear to have multiple such mutations, with no clear patterns, or genotype-phenotype correlations, yet apparent. Such mutational heterogeneity likely drives the heterogeneity of aberrant MC mediator expression, in turn causing the extreme heterogeneity of clinical presentation. Different MCAS patients can present with polar opposite clinical aberrancies. All of the body’s systems can be affected by MCAS. In addition to clinical heterogeneity, diagnosis is confounded by difficulty not only in detecting sensitive and specific biomarkers of primary MC disease but also in finding histologic evidence of a non-proliferative disease wrought by cells capable of great pleomorphism. For example, in contrast to proliferative mastocytosis which usually drives significantly elevated tryptase levels, relatively non-proliferative MCAS usually presents with normal tryptase levels; instead, histamine, MC specific prostaglandins, and other mediators need to be assessed in evaluations for MCAS. [abridged]
[Free full text]
Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal.


Author information
Division of Hematology and Hemostaseology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria.

Abstract
Activation of tissue mast cells (MCs) and their abnormal growth and accumulation in various organs are typically found in primary MC disorders also referred to as mastocytosis. However, increasing numbers of patients are now being informed that their clinical findings are due to MC activation (MCA) that is neither associated with mastocytosis nor with a defined allergic or inflammatory reaction. In other patients with MCA, MCs appear to be clonal cells, but criteria for diagnosing mastocytosis are not met. A working conference was organized in 2010 with the aim to define criteria for diagnosing MCA and related disorders, and to propose a global unifying classification of all MC disorders and pathologic MC reactions. This classification includes three types of 'MCA syndromes' (MCASs), namely primary MCAS, secondary MCAS and idiopathic MCAS. MCA is now defined by robust and generally applicable criteria, including (1) typical clinical symptoms, (2) a substantial transient increase in serum total tryptase level or an increase in other MC-derived mediators, such as histamine or prostaglandin D(2), or their urinary metabolites, and (3) a response of clinical symptoms to agents that attenuate the production or activities of MC mediators. These criteria should assist in the identification and diagnosis of patients with MCAS, and in avoiding misdiagnoses or overinterpretation of clinical symptoms in daily practice. Moreover, the MCAS concept should stimulate research in order to identify and exploit new molecular mechanisms and therapeutic targets.

PMID: 22041891 PMCID: PMC3224511 DOI: 10.1159/000328760 [Free full text]

**Mast cell disorders in Ehlers-Danlos syndrome.**

Seneviratne SL, Maitland A, Afrin L

**Author information**

Institute of Immunity and Transplantation, Royal Free Hospital and University College London, UK and Faculty of Medicine, University of Colombo, Sri Lanka

**Abstract**

Well known for their role in allergic disorders, mast cells (MCs) play a key role in homeostatic mechanisms and surveillance, recognizing and responding to different pathogens, and tissue injury, with an array of chemical mediators. After being recruited to connective tissues, resident MCs progenitors undergo further differentiation, under the influence of signals from surrounding microenvironment. It is the differential tissue homing and local maturation factors which result in a diverse population of resident MC phenotypes. An abundance of MC reside in connective tissue that borders with the external world (the skin as well as gastrointestinal, respiratory, and urogenital tracts). Situated near nerve fibers, lymphatics, and blood vessels, as well as coupled with their ability to secrete potent mediators, MCs can modulate the function of local and distant structures (e.g., other immune cell populations, fibroblasts, angiogenesis), and MC dysregulation has been implicated in immediate and delayed hypersensitivity syndromes, neuropathies, and connective tissue disorders (CTDs). This report reviews basic biology of mast cells and mast cell activation as well as recent research efforts, which implicate a role of MC dysregulation beyond atopic disorders and in a cluster of Ehlers-Danlos Syndromes, non-IGE mediated hypersensitivity disorders, and dysautonomia

PMID: 28261938 DOI:10.1002/ajmg.c.31555
Pharmacological treatment options for mast cell activation disease


Author information
Department of Oncology, Hematology and Palliative Care, Kreiskrankenhaus Waldbröl, Waldbröl, Germany.

Abstract
Mast cell activation disease (MCAD) is a term referring to a heterogeneous group of disorders characterized by aberrant release of variable subsets of mast cell (MC) mediators together with accumulation of either morphologically altered and immunohistochemically identifiable mutated MCs due to MC proliferation (systemic mastocytosis [SM] and MC leukemia [MCL]) or morphologically ordinary MCs due to decreased apoptosis (MC activation syndrome [MCAS] and well-differentiated SM). Clinical signs and symptoms in MCAD vary depending on disease subtype and result from excessive mediator release by MCs and, in aggressive forms, from organ failure related to MC infiltration. In most cases, treatment of MCAD is directed primarily at controlling the symptoms associated with MC mediator release. In advanced forms, such as aggressive SM and MCL, agents targeting MC proliferation such as kinase inhibitors may be provided. Targeted therapies aimed at blocking mutant protein variants and/or downstream signaling pathways are currently being developed. Other targets, such as specific surface antigens expressed on neoplastic MCs, might be considered for the development of future therapies. Since clinicians are often underprepared to evaluate, diagnose, and effectively treat this clinically heterogeneous disease, we seek to familiarize clinicians with MCAD and review current and future treatment approaches.

PMID: 27132234  PMCID: PMC4903110 DOI: 10.1007/s00210-016-1247-1 [Free full text]
Mast Cells, Mastocytosis, and Related Disorders.

Theoharides TC, Valent P, Akin C.

Author information
Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, and Department of Internal Medicine, Tufts University School of Medicine, Tufts Medical Center
Mastocytosis Center, Brigham and Women's Hospital, Department of Medicine, Harvard Medical School
Department of Internal Medicine I, Division of Hematology and Hemostaseology and Ludwig Boltzmann Cluster Oncology, Medical University of Vienna, Vienna.

Abstract
Mast cells, which are present in most tissues, mature in situ from hematopoietic progenitors and acquire unique features of local effector cells. These features vary, depending on the tissue microenvironment. This article provides an overview of recent developments concerning the physiology and pathobiology of mast cells. We discuss current diagnostic and therapeutic approaches to mast cell disorders, with an emphasis on mastocytosis.

PMID: 26154789 DOI: 10.1056/NEJMra1409760

See comments in:
Theoharides TC, Valent P, Akin C.

PMID: 26535528 DOI: 10.1056/NEJMc1510021
The genetic basis of mast cell activation disease - looking through a glass darkly.

Molderings GJ.

Author information
Institute of Human Genetics, University Hospital of Bonn, Sigmund-Freud-Str. 25, D-53127 Bonn, Germany. Electronic address.

Abstract
Within the last decade, and in particular since 2012, research has greatly extended our understanding of the molecular basis of systemic mast cell activation disease (MCAD). Initial studies demonstrated that somatic mutations in the tyrosine kinase KIT led to the establishment of a clonal mast cell population. Recent studies, in particular those involving next generation sequencing analyses of advanced systemic mastocytosis, have revealed mutations in additional genes. The respective genes encode proteins for various signaling pathways, epigenetic regulators, the RNA splicing machinery, and transcription factors. Although almost all of the detected mutations are somatic in nature, transgenerational transmission of MCAD appears to be quite common. However, the molecular mechanisms underlying genetic predestination, e.g. germline mutations and the contribution of epigenetic processes, still await identification. The aim of the present review is to present and discuss available genetic findings, and to outline the relationship between adult-onset systemic MCAD and childhood-onset mastocytosis, often termed cutaneous mastocytosis, on the basis of current genetic data. Finally, the implications of increased knowledge of the molecular basis of MCAD in terms of diagnostics and therapy are discussed.

PMID: 25305106 DOI: 10.1016/j.critrevonc.2014.09.001 [Free full text]
Mutational profiling in the peripheral blood leukocytes of patients with systemic mast cell activation syndrome using next-generation sequencing.

Altmüller, J., Haenisch, B., Kawalia, A., Menzen, M., Nöthen, M.M., Fier, H., Molderings, G.J.

Abstract
Mast cell activation syndrome (MCAS) and systemic mastocytosis (SM) are two clinical systemic mast cell activation disease variants. Few studies to date have investigated the genetic basis of MCAS. The present study had two aims. First, to investigate whether peripheral blood leukocytes from MCAS patients also harbor somatic mutations in genes implicated in SM using next-generation sequencing (NGS) technology and a relatively large MCAS cohort. We also addressed the question, whether some of the previously as somatic reported mutations are indeed germline mutations. Second, to identify germline mutations of relevance to MCAS pathogenesis. Here, mutation frequency in the present MCAS cohort was compared to that in public- and in-house databases in the case of frequent variants, and co-segregation was investigated in multiply affected families in the case of rare variants (allele frequency < 1%). MCAS diagnoses were assigned according to current criteria. Twenty five candidate genes were selected on the basis of published findings for SM. NGS was performed using a 76kbp custom designed Agilent SureSelect Target Enrichment and an Illumina Hiseq2000 2x100bp sequencing run. NGS revealed 67 germline mutations. No somatic mutations were detected. None of the germline mutations showed unequivocal association with MCAS. Failure to detect somatic mutations was probably attributable to the dilution of mutated mast cell DNA in normal leukocyte DNA. The present exploratory association findings suggest that some of the detected germline mutations may be functionally relevant and explain familial aggregation. Independent replication studies are therefore warranted.

PMID: 28386644 DOI: 10.1007/s00251-017-0981-y

**Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number**


**Author Information**
Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, US National Institutes of Health, Bethesda, Maryland, USA.

**Abstract**
Elevated basal serum tryptase levels are present in 4-6% of the general population, but the cause and relevance of such increases are unknown. Previously, we described subjects with dominantly inherited elevated basal serum tryptase levels associated with multisystem complaints including cutaneous flushing and pruritus, dysautonomia, functional gastrointestinal symptoms, chronic pain, and connective tissue abnormalities, including joint hypermobility. Here we report the identification of germline duplications and triplications in the TPSAB1 gene encoding α-tryptase that segregate with inherited increases in basal serum tryptase levels in 35 families presenting with associated multisystem complaints. Individuals harboring alleles encoding three copies of α-tryptase had higher basal serum levels of tryptase and were more symptomatic than those with alleles encoding two copies, suggesting a gene-dose effect. Further, we found in two additional cohorts (172 individuals) that elevated basal serum tryptase levels were exclusively associated with duplication of α-tryptase-encoding sequence in TPSAB1, and affected individuals reported symptom complexes seen in our initial familial cohort. Thus, our findings link duplications in TPSAB1 with irritable bowel syndrome, cutaneous complaints, connective tissue abnormalities, and dysautonomia.

PMID: 27749843   PMCID: PMC5397297   DOI: 10.1038/ng.3696
Characterization of Mast Cell Activation Syndrome

Afrin LB, Self S, Menk J, Lazarchick J.

Author Information
Division of Hematology, Oncology and Transplantation, University of Minnesota (UMN), Minneapolis, Minnesota.
Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, South Carolina.
Clinical and Translational Science Institute (CTSI), University of Minnesota, Minneapolis, Minnesota.

Abstract
Background: Mast cell activation syndrome (MCAS), a recently recognized nonneoplastic mast cell disease driving chronic multisystem inflammation and allergy, appears prevalent and thus important. We report the first systematic characterization of a large MCAS population.

Method: Demographics, comorbidities, symptoms, family histories, physical examination and laboratory findings were reviewed in 298 retrospective and 115 prospective patients with MCAS. Blood samples from prospective subjects were examined by flow cytometry for clonal mast cell disease and tested for cytokines potentially driving the monocytosis frequent in MCAS.

Results: Demographically, white females dominated. Median ages at symptom onset and diagnosis were 9 and 49 years, respectively (range: 0-88 and 16-92, respectively) and median time from symptom onset to diagnosis was 30 years (range: 1-85). Median numbers of comorbidities, symptoms, and family medical issues were 11, 20, and 4, respectively (range: 1-66, 2-84, and 0-33, respectively). Gastroesophageal reflux, fatigue and dermatographism were the most common comorbidity, symptom and examination finding. Abnormalities in routine laboratories were common and diverse but typically modest. The most useful diagnostic markers were heparin, prostaglandin D2, histamine and chromogranin A. Flow cytometric and cytokine assessments were unhelpful.

Conclusions: Our study highlights MCAS’s morbidity burden and challenging heterogeneity. Recognition is important given good survival and treatment prospects.

PMID: 28262205 PMCID: PMC5341697 DOI: 10.1016/j.amjms.2016.12.013
DETAILED BIBLIOGRAHY

1. Diagnostic process / General


2. Testing

PMID: 22396288 DOI: 10.1055/s-0031-1291587

PMID: 25439370 DOI: 10.1016/j.jaip.2014.06.011

PMID: 25113638 PMCID: PMC4283146 DOI: 10.1186/s12967-014-0213-2 [Free full text]

PMID: 25909362 PMCID: PMC4409380 DOI: 10.1371/journal.pone.0124912 [Free full text]
3. Treatment options

PMID: 26072665 DOI: 10.1111/ejh.12606

PMID: 25063971 DOI: 10.1016/j.coph.2014.07.002

PMID: 23666445 DOI: 10.1007/s00210-013-0880-1

PMID: 26095756 DOI: 10.1111/all.12672


PMID: 27132234 PMCID: PMC4903110 DOI: 10.1111/all.12471 [Free full text]

4. Comorbidities

PMID: 26162709 DOI: 10.1016/j.bbi.2015.07.002

PMID: 21642812 DOI: 10.1097/MAJ.0b013e31821d41dd

PMID: 25841551 DOI: 10.1016/j.iac.2015.01.010

PMID: 18662284 DOI: 10.1111/j.1478-3231.2008.01839.x


PMID: 21636142 DOI: 10.1016/j.ijcard.2011.05.007

PMID: 26775802 DOI: 10.1016/j.trsl.2015.12.012

PMID: 28261938 DOI: 10.1002/ajmg.c.31555

PMID: 15710782 DOI: 10.1161/01.HYP.0000158259.68614.40 [Free full text]
5. Genetics of MCAS

PMID: 22957768 PMCID: PMC3482677 DOI: 10.1111/j.1365-2567.2012.03627.x

PMID: 24622794 DOI: 10.1007/s00251-014-0768-3

PMID: 24472624 PMCID: PMC4016972 DOI: 10.1016/j.jaci.2013.11.039 [Free full text]

PMID: 25305106 DOI: 10.1016/j.critrevonc.2014.09.001 [Free full text]

PMID: 20838788 DOI: 10.1007/s00251-010-0474-8

PMID: 24098785 PMCID: PMC3787002 DOI: 10.1371/journal.pone.0076241 [Free full text]

PMID: 25086867 DOI: 10.1016/j.jaci.2014.06.007 [Free full text]

5.8 Molderings GJ. Transgenerational transmission of systemic mast cell activation disease-genetic and epigenetic features. Transl Res. 2016 Aug;174:86-97
PMID: 26880691 DOI: 10.1016/j.trsl.2016.01.001

5.9 Altmüller, J. et al. Mutational profiling in the peripheral blood leukocytes of patients with systemic mast cell activation syndrome using next-generation sequencing. Immunogenetics 2017.
PMID: 28386644 DOI: 10.1007/s00251-017-0981-y

5.10 Lyons, J. J. et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat. Genet 2016; 48
PMID: 27749843 PMCID: PMC5397297 DOI: 10.1038/ng.3696