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SPECIAL EDITION

THE MASTOCYTOSIS SOCIETY CHRONICLES

What's Inside...

TMS
THE MASTOCYTOSIS SOCIETY
Mast Cell Disorders

Mast Cell Disorders: Mastocytosis and Mast Cell Activation Syndromes

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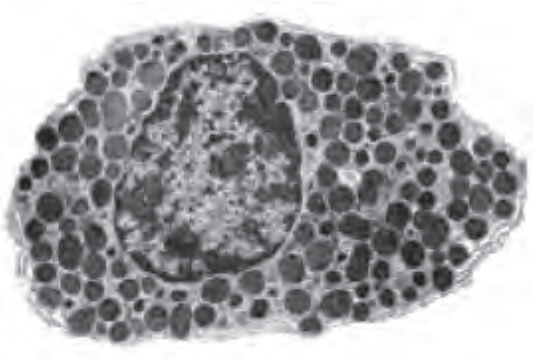

Mast Cell photo provided By Mariana Castells, MD, PhD

Overview

Mast cell disorders can cause tremendous suffering and disability due to symptomatology from daily mast cell (MC) mediator release, and/or symptoms arising from infiltration and accumulation of mast cells in major organ systems. The two major forms of mast cell disorders are mastocytosis and mast cell activation syndromes (MCAS), although it is important to note that the *process* of mast cell activation can occur with both mastocytosis and with MCAS.[1] Although systemic mastocytosis is a rare disease,[2] those suffering with MCAS have recently been increasingly recognized and diagnosed. As a result, patients with MCAS appear to represent a growing proportion of the mast cell disorder patient population.[3, 4]

MASTOCYTOSIS

Definition

Mastocytosis has been defined in the literature as an abnormal accumulation of mast cells in one or more organ systems. Broadly separated into two categories – cutaneous mastocytosis (CM) and systemic mastocytosis (SM), the disease occurs in both children and adults. CM is considered a benign skin disease representing the majority of pediatric cases. In 67-80% of pediatric cases seen, resolution will occur before or in early adulthood.[5, 6, 6a] In pediatric cases, symptoms of mast cell mediator release may occur systemically as a result of mast cell mediators released from skin lesions. This, however, does not necessarily indicate systemic disease. The incidence of systemic disease in children was previously unknown, but has now been proven to exist in some cases.[5, 6] The majority of adult patients are diagnosed with systemic disease. Skin involvement, typically urticaria pigmentosa, is common in adult patients and can provide an important clue to accurate diagnosis.[7]

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Special Edition For Health Care Professionals

The Mastocytosis Chronicles is distributed to the members of the Mastocytosis Society, Inc. on a quarterly basis.

This special edition of *The Mastocytosis Chronicles* has been published specifically for physicians and health care professionals. This edtion contains diagnostic and treatment protocols for mastocytosis and mast cell activation disorders, locations of mast cell disorder treatment centers, physician contact information, documentation of research articles, and other pertinent information. For additional information visit *www.tmsforacure.org.*

The Mastocytosis Society, Inc. Mission

The Mastocytosis Society, Inc. is a 501(c)3 nonprofit organization dedicated to supporting patients affected by Mastocytosis or Mast Cell Activation Disorders, as well as their families, caregivers, and physicians through research, education, and advocacy.

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The Mastocytosis Society is a long-standing member of the National Organization for Rare Disorders (NORD)

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Diagnosis and Classification

CM is diagnosed by the presence of typical skin lesions and a positive skin biopsy demonstrating characteristic clusters of mast cells. The preferred method of diagnosing SM is via bone marrow (BM) biopsy. The World Health Organization (WHO) has established criteria for diagnosing SM, summarized[8] as follows:

Major[a]: Multifocal dense infiltrates of mast cells (MCs) (>15 MCs in aggregate) in tryptase stained biopsy sections of the bone marrow or other extracutaneous organ.

Minor[a]:

- More than 25% of MCs in bone marrow or other extracutaneous organ(s) show abnormal morphology (i.e. are atypical MC type 1 or are spindle–shaped MCs) in multifocal lesions in histologic examination
- *KIT* mutation at codon 816[b] in extracutaneous organ(s) (in most cases bone marrow cells are examined)
- *KIT*$^+$ MCs in bone marrow show aberrant expression of CD2 and/or CD25
- Serum total tryptase > 20 ng/mL (does not count in patients who have AHNMD-type disease.)

Abbreviation Key:

KIT: KIT tyrosine kinase receptor
MC(s): Mast cells
AHNMD: associated (clonal) hematologic non-mast cell lineage disease

[a] If at least one major criterion and one minor criterion OR at least three minor criteria are fulfilled, the diagnosis of systemic mastocytosis can be established.

[b] Activating mutations at codon 816, in most cases, *KIT D816V.*

Diagnostic techniques differentiate mastocytosis into the following categories:

CUTANEOUS MASTOCYTOSIS

This category includes maculopapular cutaneous mastocytosis/urticaria pigmentosa (UP), telangiectasia macularis eruptiva perstans (TMEP), diffuse cutaneous mastocytosis (DCM), and solitary mastocytoma, although these categories are under review and revision.[9] Most cases of pediatric mastocytosis fall into one of these categories and may or may not include symptoms of systemic mast cell activation as a result of mediators released from the skin (see *Pediatric Mast Cell Disorders Fact Sheet* in this issue). It should be noted that the term "UP" encompasses a variety of clinical manifestations. In children, some of these varieties will fade away, some will develop into indolent systemic mastocytosis and some will evolve into a newly described entity called well-differentiated systemic mastocytosis.[5]

SYSTEMIC MASTOCYTOSIS

Systemic mastocytosis consists of a group of rare, heterogeneous disorders involving growth and accumulation of abnormal mast cells in one or multiple extracutaneous organ systems (Table 1). Standard technique can be used to obtain an iliac crest bone marrow (BM) biopsy and aspirate smear for diagnosis. Aspirated BM should be allocated for flow cytometry to assess for the presence of mast cells with aberrant phenotype (i.e., co-expression of CD25). Immunohistochemistry for *KIT*, mast cell tryptase, and CD25 should be performed on sections of the biopsy.[10-14]

TABLE 1.
Major Variants of Systemic Mastocytosis[15]

ISM (Indolent systemic mastocytosis)
WHO criteria for SM met, MC burden low, +/- skin lesions, no C findings, no evidence of AHNMD
• **Bone marrow mastocytosis:** ISM with BM involvement, but no skin lesions
• **Smoldering SM:** ISM, typically with skin lesions, with 2 or more B findings, but no C findings.
SM-AHNMD (SM with associated clonal hematologic non mast cell lineage disease)*
Meets criteria for SM *and also* criteria for an AHNMD (MDS, MPN, MDS/MPN, AML), or other WHO-defined myeloid hematologic neoplasm, +/- skin lesions.
ASM (Aggressive systemic mastocytosis)
Meets criteria for SM with one or more C findings. No evidence of MCL, +/- skin lesions.
MCL (Mast cell leukemia)
Meets criteria for SM. BM biopsy shows a diffuse infiltration, usually compact, by atypical, immature MCs. BM aspirate smears show 20% or more MCs. Typical MCL: MCs comprise 10% or more of peripheral blood white cells. Aleukemic MCL: < 10% of peripheral blood white cells are MCs. Usually without skin lesions.

* A lymphoproliferative disorder or plasma cell dyscrasia may rarely be diagnosed with SM.

BM: bone marrow

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TABLE 2.
***B* and *C* Findings[15]**

***B* Findings**
BM biopsy showing > 30% infiltration by MCs (focal, dense aggregates) and serum total tryptase level > 200 ng/mL
Myeloproliferation or signs of dysplasia in non–MC lineage(s), no prominent cytopenias; criteria for AHNMD not met
Hepatomegaly and/or splenomegaly on palpation without impairment of organ function and/or lymphadenopathy on palpation/imaging (> 2 cm)
C* Findings
Cytopenia(s): ANC < 1 x 10^9/L, Hb < 10 g/dL, or platelets < 100 x 10^9/L
Hepatomegaly on palpation with impairment of liver function, ascites, and/or portal hypertension
Skeletal lesions: osteolyses and/or pathologic fractures
Palpable splenomegaly with hypersplenism
Malabsorption with weight loss from gastrointestinal tract MC infiltrates

* Must be attributable to the MC infiltrate.

Indolent Systemic Mastocytosis

The majority of adult patients fit into this category, fulfilling the criteria for indolent systemic mastocytosis (ISM).[9, 11, 16, 17] The bone marrow, gastrointestinal tract, skeletal system, nervous system and skin may be affected. Some patients may have enlarged livers and spleens and lymphadenopathy. Mediator-related symptoms are common, but the grade of bone marrow infiltration is low (usually less than 5 percent) with the bone marrow fulfilling the criteria for SM and 80-90% of the patients exhibiting a positive D816V KIT mutation. In most patients the serum tryptase concentration exceeds 20 ng/mL, but a normal level of tryptase does not rule out either mastocytosis or another mast cell activation disorder. Treatment usually includes mediator-targeting drugs, including antihistamines, but does not usually require cytoreductive agents, although there are exceptions.

Isolated bone marrow mastocytosis (BMM) and smoldering systemic mastocytosis (SSM) are variants of indolent SM[17]. BMM is characterized by the absence of skin lesions, lack of multiorgan involvement, and an increased incidence of anaphylaxis.[18] In SSM, two or more B findings (Table 2) are found and there is a greater possibility that the disease will progress to a more aggressive variant.

Well differentiated SM (WDSM), first described in 2004[19], is reported in the literature as a form of systemic mastocytosis that fulfills the major criterion for SM and continues to be studied by researchers.[5, 6] A relatively frequent form of mastocytosis in children, it usually has a pediatric onset, nodular or plaque skin lesions, possibly extensive, severe mast cell symptoms and goes into adulthood in a low percentage of cases. The mast cells do not have the CD25 marker that is part of the minor WHO criterion for SM and roughly 90% of WDSM patients don't have the c-kit D816V marker or other exon 17 c-kit mutations. Bone marrow analysis identifies mast cells in WDSM patients as notably large, round, mature-appearing mast cells with the absence of the spindle-shaped mast cells typically seen in SM.[5] Baseline serum tryptase levels in these patients are usually lower than what is frequently detected in SM, except in a variable percentage of children at onset. Imatinib mesylate has been used in some patients with severe cases of WDSM, since these patients do not usually carry the c-kit D816V mutation, which causes resistance to imatinib.[20]

Recent Updates In Diagnosis

A new diagnostic algorithm has been proposed by the European Competence Network on Mastocytosis for evaluating patients with suspected mastocytosis.[20a] Recommendations for KIT mutation analysis, including in peripheral blood, have also been recently published.[20b]

Systemic Mastocytosis with Associated Clonal Hematologic Non-Mast Cell Lineage Disease (AHNMD)

These patients fit the criteria for SM and they fit the WHO criteria for myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), MDS/MPN, or acute myeloid leukemia (AML), with or without skin lesions.[15, 21, 22]

Aggressive Systemic Mastocytosis

In this rare variant, aggressive systemic mastocytosis (ASM) patients fit the criteria for SM, and their bone marrow biopsy reveals abnormal blood cell formation that does not fit WHO criteria for an AHNMD, as listed above,[15] with or without skin lesions.

Mast Cell Leukemia

In this rare variant, mast cell leukemia (MCL) patients fit the criteria for SM, and a bone marrow aspirate smear shows that 20% or more of the cells are mast cells, or 10% or more mast cells are seen in circulating blood.[15, 23] The mast cells have malignant features. Prognosis is poor, although life expectancy has been extended, in some cases, due to advances in cytoreductive therapy.

Mast Cell Sarcoma

Mast cell sarcoma is a rare tumor and prognosis is generally very poor. Pathological examination of the tumor has shown it to be highly malignant with an aggressive growth pattern.[24, 25] Patients with this tumor do not fulfill the criteria for SM. The imatinib mesylate-resistant KIT D816V mutation has not been found in reported mast cell sarcomas, such that use of imatinib has been attempted in some patients.[25]

Diagnostic Workup for Aggressive Variants or Associated Hematological Disorder[10, 15, 26]

When aggressive disease or an associated hematological disorder is suspected, further evaluation of the patient may include:

1. Comprehensive bloodwork;

2. X-ray or CT scan of the chest, looking for evidence of significantly enlarged lymph nodes (greater than 2 cm in diameter);

3. X-ray or nuclear medicine bone scan of the skeletal system, looking for osteoporosis, osteosclerosis, or areas where calcium has been completely lost from bone;

4. CT scan or ultrasound of the abdomen, looking for enlarged liver or spleen, enlarged lymph nodes, or the collection of fluid;

5. Endoscopy/colonoscopy and biopsy of the gastrointestinal tract, looking for evidence of mast cell infiltration, ulcers, or areas of bleeding. Mast cell infiltration can be identified by aggregates of 15 or more abnormal mast cells, or sheets of mast cells. Abnormal mast cells can be identified by the presence of CD25 on these cells.[27] Other tests may be done, as indicated, if there is a suspected hematologic disorder or to evaluate the individual patient's symptoms. By contrast, further testing should be kept to a minimum when the disease seems to be confined to the skin, and in most pediatric cases.

Mast Cell Activation and Triggers

Mast cells can be activated through both IgE and non-IgE-related mechanisms, resulting in the release of mediators, such as tryptase, histamine, heparin, leukotrienes and prostaglandins.[28] Triggers of mediator release may include: heat; cold; temperature change; foods; medications; alcohol; friction; environmental, emotional, or physical stress; perfumes/odors; viral/bacterial/fungal infections; venoms; and fatigue. Some patients may experience reactions to medications including, but not limited to: opiates, antibiotics and NSAIDs. Use with caution. Mast cell activation can occur along with, or independent of, any form of mastocytosis.

Mast Cell Mediator Symptoms

The myriad symptoms patients experience during mast cell activation/degranulation can wreak havoc on patients on a daily basis, and multiple organ systems, including pulmonary, cardiovascular, dermatologic, gastrointestinal, musculoskeletal, and neurologic can be involved.[3, 4, 28-32] Symptoms may include, but are not limited to: flushing of the face, neck, and chest; headache; tachycardia and chest pain; abdominal pain, bloating, GERD, diarrhea, vomiting; uterine cramps or bleeding; rashes, including UP, TMEP; bone/muscle pain, osteosclerosis, osteopenia, osteoporosis; itching, +/- rash; blood pressure instability; brain fog, cognitive dysfunction; anxiety/depression; lightheadedness, syncope; and anaphylaxis. These symptoms may appear as acute (as in anaphylaxis) or as chronic conditions. It should be noted that the manifestation of anaphylaxis or similar symptoms among infants and preschoolers may be more difficult to identify.

Treatment of Mediator Release Symptoms

Treatment of mastocytosis depends on the symptoms and the classification of disease.[6, 9, 33] Symptoms of mediator release are treated with H1 and H2 antihistamines, mast cell stabilizers, leukotriene inhibitors, and possibly aspirin (under ***direct supervision*** of a physician). All mast cell disease patients should carry two doses of injectable epinephrine unless otherwise contraindicated (Glucagon may need to be administered for patients on beta-blockers). Patients

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should also be instructed on how to self-administer epinephrine while in a recumbent position, to maximize rapid absorption of the drug.

Perioperative Management

While the incidence of hypersensitivity to anesthesia and surgical procedures in patients with mast cell disorders is unknown, various non-specific triggers in the perioperative setting may cause mast cell degranulation, and thus immediate hypersensitivity. Therefore, the goal of all perioperative management is prevention of mast cell mediator release. This can be accomplished by careful history taking, excellent communication between the anesthesia and surgical staff, avoidance of all known and potential triggers of mediator release, and careful attention to management of perioperative mast cell degranulation and/or cardiovascular changes.[34] Although perioperative complications due to mast cell mediator release in children with mastocytosis are rare, they are not unknown.[6] Measures to prevent triggering mast cell degranulation in adults and children should be utilized whenever possible.

Prevention also includes perioperative antianxiety medications to avoid precipitating mast cell degranulation; maintenance of a steady environmental temperature throughout the entire surgical experience; minimizing friction and mechanical trauma (i.e. tape, tourniquet use, etc.) near mastocytosis skin lesions; careful positioning of the patient, being mindful of possible osteoporosis or osteolysis; avoiding histamine releasing drugs such as atracruium and mivacurium; pre-treating to prevent nausea and vomiting; aggressive treatment of pain, which is a potent mast cell degranulator, including utilizing some acceptable forms of opioids (i.e. fentanyl); use of H1/H2 receptor antagonists to maintain mast cell stability.[34, 34a]

Ring and Messmer have developed a grading scale[34, 35] to describe clinical severity of perioperative immediate hypersensitivity in mastocytosis:

Usually Non-Life Threatening

Grade I: Mucocutaneous signs and symptoms only

Grade II: Mild mucocutaneous signs, features which may be associated with cardiovascular and respiratory changes.

Life-Threatening

Grade III: Cardiovascular collapse which may be associated with mucocutaneous and/or gastrointestinal signs, and/or bronchospasm.

Grade IV: Cardiac arrest

Specific management of a mast cell degranulation event in patients with mast cell disorders includes stopping any suspicious drug being administered, discontinuation of anesthetic agents likely to cause vasodilation and negative muscular contractility, if possible, and early administration of epinephrine for Grade III and Grade IV reactions along with 100% oxygen and large volume fluid support.

With these measures, patients with mast cell disorders can be prepared for surgery with a plan that includes preventing mast cell degranulation by identification of possible triggers, rapid recognition of degranulation when it does occur and immediate appropriate intervention.

Advanced Disease Considerations and Treatment

Advanced disease symptoms may include: anemia, thrombocytopenia, ascites, bone fractures, gastrointestinal abnormalities, and enlargement of the liver, spleen, and lymph nodes, which ultimately can lead to organ failure and early death. Therapies exist for advanced SM, and promising new treatments are being developed. Prominent among these are tyrosine kinase inhibitors (TKIs) targeting the *KIT* kinase[36, 37a] (e.g., midostaurin[36]). Imatinib is approved therapy for adult ASM patients lacking the KIT D816V mutation or if mutation status is unknown. Standard therapies for ASM are interferon and the chemotherapeutic agent cladribine, employed with antimediator therapy, to reduce disease burden and control symptoms. In patients with SM-AHNMD, therapy selection usually depends on the associated disease, which is commonly more aggressive than the SM part. MCL requires a polychemotherapy approach.

Prognosis

All patients with mastocytosis are at increased risk

for anaphylaxis and potentially a poor outcome. The prognosis of mastocytosis depends on the specific classification of disease.[17] The prognoses for cutaneous mastocytosis and indolent mastocytosis are good. Most patients with SM have ISM. ISM patients have preserved organ function and their survival is comparable to that of the general population. Patients with smoldering SM may have an increased risk of developing disease transformation to aggressive forms of SM. Survival of patients with more advanced SM is significantly shorter than that of the overall population and is affected by disease subtype. Reported 2009 median survival was 41 months for ASM, 24 months for SM-AHNMD, and 2 months for MCL.[26] Patients with ASM suffer debilitating symptoms and have signs of organ dysfunction (C-findings; Table 2). In patients with SM-AHNMD, prognosis can differ depending on the particular myeloproliferative neoplasm.[37b]

MAST CELL ACTIVATION SYNDROMES

Definition

Existence of a subset of mast cell disorder patients who experience episodes of mast cell activation without detectable evidence of a proliferative mast cell disorder was postulated over 20 years ago.[38, 39] Over the last two decades, with development of improved methodology for identification of abnormal mast cells,[40-43] it became apparent that there were patients who exhibited symptoms of mast cell mediator release who did not fulfill the criteria for SM.[44, 45] Thus began the evolution of discussions about other forms of mast cell disorders, both clonal and nonclonal, which became known as Mast Cell Activation Syndromes (MCAS).[46, 47]

Diagnosis and Proposed Classification

Recognition by specialist physicians of the importance of mast cell activation in disease led to an international Mast Cell Disorders Working Conference emphasizing this topic in September of 2010. Consensus statements were published regarding classification of and diagnostic criteria for mast cell disorders,[1] where mast cell activation plays a prominent role.

As previously stated, mediators produced by mast cells have a considerable effect on specific symptomatology. Symptoms, including, but not limited to flushing, pruritis, urticaria, headache, gastrointestinal symptoms (including diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux), and hypotension, allow a patient to meet the *first* of *three required co-criterion* for systemic mast cell activation when the patient exhibits symptoms involving two or more organ systems in parallel, which are "recurrent or permanent, cannot be explained by other known disorders/conditions (other than mast cell activation), and require a therapeutic intervention."[1]

The *second* required co-criterion for systemic mast cell activation depends on documentation that mast cells are directly involved in the symptomatology. An increase in the serum level of tryptase, above baseline and within a narrow (generally accepted as one to two hour) window of time after a symptomatic episode, is proposed as the preferred method for providing evidence of mast cell involvement according to these criteria.[1, 48, 49] The consensus article provides a method for calculating the required minimum rise in serum tryptase.[1] Consensus members also agreed that when serum tryptase evaluation is not available or when the tryptase level does not rise sufficiently to meet the required increase for the co-criterion, other mediator tests could suffice. A rise in urinary n-methyl histamine, prostaglandin-D_2, or its metabolite, 11β-prostaglandin-$F_{2\alpha}$ (24-hour urine test for any of the three), is considered an alternative for the co-criterion related to a requirement for a mast cell mediator level rise during a systemic mast cell activation event.[1]

Finally, the *third* co-criterion requires a response (based on response criteria[10]) to medications that inhibit the action of histamine.[1] In addition, a "complete or major" response to drugs that inhibit other mediators produced by mast cells or block mast cell mediator release can be regarded as fulfillment of the third co-criterion for MCAS.

PRIMARY MCAS

Primary MCAS results from a clonal population of mast cells and may be due to mastocytosis or monoclonal Mast Cell Activation Syndrome (MMAS). Primary MCAS with mastocytosis can be diagnosed if the patient has symptoms of mast cell activation and fulfills the WHO criteria for mastocytosis. MMAS is a new, distinct disease[50] characterized by the presence of abnormal mast cells and fulfillment of criteria for mast cell activation, but where sufficient criteria for a diagnosis of mastocytosis are not identified.[1, 3, 10, 32, 44, 45, 50-52]

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SECONDARY MCAS

Secondary MCAS[1, 3, 32, 53] is diagnosed when mast cell activation occurs as an indirect result of another disease or condition. Physician awareness of the presence of secondary MCAS will allow for more appropriate mast cell activation-targeted treatments, in addition to primary disease-related medications, to be provided. In addition to the widespread example of atopy as a cause of secondary MCAS, other diseases that can cause secondary MCAS have been reviewed in the literature.[1, 3, 53]

IDIOPATHIC MCAS

Idiopathic MCAS is proposed as a final diagnosis after proposed mast cell activation criteria have been fulfilled and a thorough evaluation has excluded the possibility of another known underlying cause for this activation.[1, 54] Idiopathic MCAS is therefore nonclonal, with regard to current diagnostic capabilities related to mast cell analyses, and has been presented and discussed in the literature by a variety of mast cell disorder specialists.[1, 3, 32, 50, 53-55] Review of other causes of MCAS to aid physicians in evaluation for the exclusionary diagnosis of idiopathic MCAS have also been provided.[1, 3, 50]

Triggers, Symptoms, Perioperative Management and Treatment of MCAS

MCAS, in all of its forms, can cause tremendous suffering and disability due to symptomatology from daily mast cell mediator release. The triggers, symptoms and treatment of MCAS are similar to those listed above for mastocytosis symptoms *related to mast cell activation and mediator release*.[50, 54, 56] Perioperative management, as listed above for mastocytosis, should also be a consideration.

Additional Considerations for MCAS

It is recognized by researchers that current diagnostic methods for capturing a rise in mast cell mediators after a symptomatic episode are not ideal.[54, 57, 58] Some patients who present with typical and recurrent signs and symptoms of mast cell activation do not present with elevated levels of mediators for which we are currently able to test. Non-specialist physicians may most commonly use serum tryptase levels to exclude a mast cell disorder. However, some MCAS specialists have indicated that tryptase rises are not seen as often in patients with certain forms of MCAS, and that other changes in bloodwork and urine tests can sometimes be more reliable.[55, 57] Additionally, there is a very narrow window of time (1-2 hours after symptoms begin) during which to obtain a serum tryptase test to indicate mast cell activation,[1] such that obtaining laboratory evidence of the event can prove difficult in many circumstances. Cardet *et al.* suggest that, despite lack of proof of elevated mast cell mediators, a response to mast cell or mast cell mediator blockers should be determined in such patients.[54] If a patient responds well to treatment, a diagnosis of idiopathic MCAS remains open for consideration, as long as other diagnoses continue to be considered.

Dr. Afrin notes that even the co-criterion requiring a response to mast cell targeted therapy can be lacking in some patients. In his experience with more than 300 MCAS patients, diagnostics are not always useful for guiding specific choices for anti-mediator therapy, such that multiple mast cell (or mast cell mediator) blocking therapies must be tried before successful symptom resolution is attained.[4] Also, in recent work by Picard *et al*., it is reported that only one third of MCAS patients experience a complete resolution with treatment; one third have a major response and another third have a minor response, and a combination of drugs is usually required to achieve control of symptoms.[50]

Prognosis

All patients with MCAS are at increased risk for anaphylaxis and a potentially poor outcome. Prognosis will likely depend on the type of MCAS. As MMAS is a newly described entity, no long-term prognostic data are available. The long-term prognosis for patients with idiopathic MCAS is similarly unknown. For secondary MCAS, the prognosis likely depends on the primary condition causing the MCAS.

CONCLUSIONS

Recognition of mast cell disorders can be difficult due to the many possible presentations, often leading to deferment of proper diagnosis and treatment.[4, 26, 50, 55, 59] In addition, due to the broad range of signs and symptoms, patients with mast cell disorders may be misdiagnosed.[1, 4, 11] Awareness of the existence of mastocytosis and mast cell activation syndromes can help physicians recognize potential mast cell disorder patients for further evaluation,[50] provide for more accurate diagnoses and would allow for more rapid and effective treatment allocation.

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The Mastocytosis Society Survey on Mast Cell Disorders:
Patient Experiences and Perceptions

Susan Jennings, PhD, Nancy Russell, Dr PH, Blair Jennings, BS, Valerie Slee, RN, BSN, Lisa Sterling, BS, Mariana Castells, MD, PhD, Peter Valent, MD and Cem Akin, MD, PhD

J Allergy Clin Immunol Pract. 2014;2(1):70-6.

In 2014, The Mastocytosis Society, Inc. (TMS) presented the first set of results from the 2010 Mast Cell Disorder Patient Survey (see above reference). The article and its online repository (containing additional data and the original survey questionnaire) are available free to the public through the journal's website (**www.jaci-inpractice.org**). The authors are currently preparing a second TMS Survey report, focusing on clinical experiences, co-morbidities and additional concerns. A poster of this second report was presented during the 2015 American Academy of Allergy, Asthma and Immunology Annual Meeting (available at www.eposters.net).

Background

In December of 2009, Dr. Cem Akin of Harvard Medical School and Brigham and Women's Hospital contacted TMS about a unique opportunity for patients to provide input into the establishment and/or revision of the diagnostic criteria for mastocytosis and the disorders of mast cell activation. He asked TMS to create a survey, based on a series of questions originally provided by Dr. Peter Valent of the Medical University of Vienna. Patients in Europe were invited to do a similar survey based on the same questions.

A web-based survey was designed and implemented by TMS. Patients of all ages, or caregivers on the patients' behalf, living in or outside the United States (U.S.), with cutaneous or systemic mastocytosis, mast cell activation syndrome or any other suspected mast cell disorder, were invited to complete the survey whether or not they were members of TMS. The survey was posted through the TMS website between April 15 and May 24, 2010.

Information collected included survey respondents' demographics, diagnoses, symptoms, medications, comorbid conditions, clinical and laboratory tests, allergies, triggers of mast cell symptoms, dietary concerns, occurrence of mast cell disease in their families, its impact on their lives and their perceptions of mast cell related care in the United States.

The TMS Patient Survey provides an example of patients and specialists working together to learn from the experiences and perceptions of people coping with rare disorders. Survey results provide useful information for non-specialist clinicians who treat or collaborate in the treatment of these patients and for patients to review experiences of others with mast cell disorders.

ICD-10-CM Progress Report

January 2016

Tenth Edition of the International Classification of Diseases-Clinical Manifestation (ICD-10-CM) Code Set for Mast Cell Activation Syndromes and Mastocytosis

The Mastocytosis Society, Inc. (TMS), chaired by Valerie Slee, RN, BSN, and the American Academy of Allergy, Asthma and Immunology (AAAAI) Mast Cell Disorder (MCD) Committee, chaired by Joseph Butterfield, MD, have joined forces to help create medical codes for Mast Cell Activation Syndromes (MCAS) and update existing codes for Mastocytosis. The two organizations formed a subcommittee consisting of AAAAI MCD Committee and TMS Research Committee members, chaired by Arnold Kirshenbaum, MD, and Catherine Weiler, MD, PhD, for the MCD Committee, and Susan Jennings, PhD, and Nancy Russell, DrPH, for TMS, to work on the collaborative development of proposals for new and updated Tenth Edition International Classification of Diseases-Clinical Manifestation (ICD-10-CM) codes for mast cell disorders. A proposal to add MCAS codes to ICD-10-CM was then jointly submitted to the National Center for Health Statistics (NCHS; housed at the Center for Disease Control and Prevention) in January 2014 and a second proposal, focused on modification and expansion of existing Mastocytosis ICD-10-CM codes, was jointly submitted to the NCHS in July 2014. Both proposals were also co-sponsored and approved by the AAAAI Board of Directors. The MCAS ICD-10-CM proposal was presented at the March 19-20, 2014 ICD-10 Coordination and Maintenance Committee Meeting of the Centers for Disease Control and Prevention. The Mastocytosis ICD-10-CM proposal was presented at the September 23-24, 2014 ICD-10 Coordination and Maintenance Committee Meeting. Regular updates to ICD-10 are currently scheduled to begin on October 1, 2016.

MCAS and Mastocytosis ICD-10-CM Subcommittee Members:

Joseph Butterfield, MD, Co-Director of the Mayo Clinic Center of Excellence for Mast Cell and Eosinophil Disorders; Chair, AAAAI Mast Cell Disorders Committee

Arnold Kirshenbaum, MD, Co-Chair, MCAS and Mastocytosis ICD-10-CM Subcommittee (MCD Committee)

Catherine Weiler, MD, PhD, Co-Director of the Mayo Clinic Center of Excellence for Mast Cell and Eosinophil Disorders; Co-Chair, MCAS and Mastocytosis ICD-10-CM Subcommittee (MCD Committee)

Cem Akin, MD, PhD, Director of the Mastocytosis Center of Excellence at Brigham and Women's Hospital and Dana-Farber Cancer Institute

Dr. Mariana Castells, MD, PhD, Associate Director of the Mastocytosis Center of Excellence at Brigham and Women's Hospital and Dana-Farber Cancer Institute

Susan Jennings, PhD, Co-Chair, Research Committee, The Mastocytosis Society, Inc.; Co-Chair, MCAS and Mastocytosis ICD-10-CM Subcommittee (TMS)

Nancy Russell, Dr. PH, Co-Chair, Research Committee, The Mastocytosis Society, Inc.; Co-Chair, MCAS and Mastocytosis ICD-10-CM Subcommittee (TMS)

Valerie Slee, RN, BSN, Chair, Board of Directors and Board of Directors Liaison to the Research Committee, The Mastocytosis Society, Inc.

Mishele Cunningham, RN, BSN, PHN, Chair, Education Committee, The Mastocytosis Society, Inc.

The Mastocytosis Society

Pediatric Mast Cell Disorders Fact Sheet

By, Valerie Slee RN, BSN, and Mishele Cunningham RN, BSN, PHN

Pediatric mast cell disorders, a group of rare diseases, are characterized by either the presence of too many mast cells in the skin or other tissues (pediatric mastocytosis), or recurrent symptoms arising from release of mast cell mediators in two or more organ systems, in parallel (mast cell activation syndrome, MCAS). Mast cells are instrumental in mediating anaphylaxis, and children with mast cell disorders are at higher risk to develop both provoked and unprovoked episodes of anaphylaxis. A child whose disease appears to be confined to the skin may still exhibit systemic symptoms due to mast cell degranulation and mediator release.[1] Symptoms common to pediatric mastocytosis and MCAS include flushing of the face and neck, dermatographism, gastrointestinal complaints [such as diarrhea, abdominal pain, nausea, gastroesophageal reflux (GERD)], pruritis, dyspnea, headache, lethargy, fatigue, and neuropsychiatric symptoms. Many children may not complain of specific symptoms, may not be able to identify or localize a symptom, or may have every symptom, while others may have very few or none.

Age of Onset:

- Pediatric mastocytosis is commonly diagnosed prior to age two.
  - Pediatric disease is seen at a ratio of 1.4 males:1 female.[1a]
  - No race has been found to be predominant.[2]
- Pediatric mast cell activation syndrome can be diagnosed at any age.

Presentation:

- In 90% of the cases, the typical presentation involves cutaneous manifestations (skin lesions).

These may include:

Solitary or Multiple Mastocytomas

- Usually present at birth
- Solitary, elevated lesion which usually resolves during childhood
- Multiple mastocytomas may evolve into adult well differentiated systemic mastocytosis (WDSM)[1]

Urticaria Pigmentosa/Maculopapular Cutaneous Mastocytosis (UP)

- Red maculopapular lesions tend to wheal when scratched (positive Darier's sign)
- Blister formation can occur with rubbing or stroking of lesion and is associated with pruritis[2]
- Encompasses several clinical entities with different outcomes, including: pitted melanotic macules, reddish brown telangiectatic macules, lightly pigmented papules, brownish papules, and small nodules

Diffuse Cutaneous Mastocytosis (DCM)

- Skin thickened, hyperpigmented and diffusely infiltrated; can involve up to 100% of the skin with the central area, head and scalp heavily affected
- Can appear at birth or early infancy
- Blisters, some of which are hemorrhagic; bullae are present and dermatographism may be prominent
- Flushing is a common symptom
- Tryptase may be elevated due to increased mast cell burden in the skin, and can be indicative of well differentiated systemic mastocytosis

Possible Symptoms

- Itching
- Flushing
- Darier's Sign and dermatographism
- Abdominal pain, nausea, diarrhea, bloating, colic in infants, GERD
- Bone and joint pain
- Headache
- Fatigue
- Neuropsychiatric symptoms, such as: brain fog, ADD/ADHD, irritability, behavioral issues, seizures
- Anaphylaxis

Guidelines for Acquiring a Diagnosis:

- Completion of a thorough patient history
- Careful skin examination and biopsy of lesions with mast cell stains (hematoxylin, eosin, giemsa stains) and immunohistochemistry for tryptase and KIT
- Acquisition of labs, including complete blood count, peripheral smear, serum chemistry, serum tryptase and liver function tests
- Exam of liver and spleen for hepatosplenomegaly by ultrasound or scan
- Any other exam relevant to individual symptoms (endoscopy, colonoscopy, bone scan, etc.)
- Bone marrow biopsy and aspirate with flow cytometry, only if clinical suspicion of systemic or progressive disease:
  - abnormal peripheral blood counts, organomegaly, significant lymphadenopathy, severe recurrent systemic mast cell mediator-related symptoms, persistent high tryptase, persistence of disease into adulthood[2, 3]

Triggers to Avoid (varies by patient):

- Changes in temperature, heat and cold
- Friction or pressure on the skin
- Specific foods: very individualized but may include shellfish, high histamine foods such as left-overs, salicylate-containing foods, nuts, peanuts and other potential allergens
- Medications, which can be problematic, include: opioid narcotics, alcohol as an additive, IV vancomycin, neomycin, benzocaine, anti-cholinergics, and certain anesthetics.[3a] See Emergency Protocol at www.tmsforacure.org
- Insect bites and stings, jellyfish, snake and fire ant venoms
- Physical, emotional or environmental stressors and fatigue
- Perfumes, odors and chemical exposures

Treatment Guidelines:

- Avoidance of triggers
- H1 and H2 antihistamines
  - H1: loratadine, cetirizine, desloratadine, diphenhydramine, hydroxyzine, fexofenadine, chlorpheniramine maleate, doxepin
  - H2: ranitidine, cimetidine, famotidine
- Leukotriene inhibitors
  - Montelukast, zileuton, zafirlukast
- Mast cell stabilizers
  - Oral cromolyn sodium
  - Ketotifen
- Injectable epinephrine
  - Auvi Q: talking auto injector
  - EpiPen auto injector
- Topical treatments
  - Steroid creams
  - Cromolyn sodium cream 1%-5%
- No chemotherapy is indicated in cutaneous or indolent systemic disease in children, unless indicators of progression to aggressive disease are identified

Prognosis:

- Benign course will be seen in approximately 70% of patients.[1]
- Approximately 30% of pediatric mastocytosis cases persist into adulthood.[1]
- Children with extensive bullous lesions appear to be at increased risk of shock or sudden death from anaphylaxis.[4]
- Children with widespread skin lesions (UP & DCM) are at increased risk for severe systemic reaction due to potential mast cell mediator release from affected skin.[4]

Support Services:

- The Mastocytosis Society is a 501(c)3 nonprofit organization dedicated to supporting patients affected by Mastocytosis or Mast Cell Activation Disorders, as well as their families, caregivers, and physicians through research, education and advocacy.
- The Mastocytosis Society coordinates support groups in nearly every state. Please visit our website at **www.tmsforacure.org.**
- Mastokids.org is a site where parents and caregivers of children with mastocytosis or mast cell disease can come to learn, find support, and discover a safe environment to interact with other families.

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Pediatric Mastocytosis Fact Sheet

Mission and History of TMS

Mission: The Mastocytosis Society, Inc. is a 501(c)3 nonprofit organization dedicated to supporting patients affected by Mastocytosis or Mast Cell Activation Disorders as well as their families, caregivers, and physicians through research, education, and advocacy.

History: The Mastocytosis Society, Inc. (TMS) was founded in 1995 by Bill Abbottsmith, Linda Buchheit, Olive Clayson, Iris Dissinger, Bill Hingst, and Joe Palk. At that time very little was known about Mastocytosis, so these pioneering individuals sought to fill a massive void with some answers to their multitude of questions about this rare disease. They found one another through NORD, sheer determination and extensive research.

The first support group meeting was held in Baltimore at the Inner Harbor in 1994 and was attended by Linda Buchheit and Bill Hingst. The second meeting was held the following year at Linda Buchheit's home in Ohio. Fourteen members attended that year. Little did they know how fruitful their efforts would be and what a lifeline they would become as more and more patients joined each year!

Until 1990 many patients diagnosed with Mastocytosis were given a very grim prognosis. Up until that time, Mastocytosis was not often considered when physicians were making a differential diagnosis, and many cases were completely missed, resulting in patient death. At that point, signs of the disease were then discovered on autopsy; however, because so little was known about Mastocytosis, it was presumed that Mastocytosis was one of the causes of death, when in fact the patient had often died of other causes, and the Mastocytosis was an incidental finding! On the other hand, more advanced cases of aggressive Mastocytosis were also recognized during post-mortem exams, leading pathologists to identify all forms of Mastocytosis as having a high associated mortality rate. Fortunately, that prognosis has improved as more patients are diagnosed and treated sooner, and more physicians research and treat this disease. Today, we know that pediatric patients have greater than a 75% chance of outgrowing their disease at or before puberty, and adults with Indolent Systemic Mastocytosis can have a near normal life expectancy if they avoid triggers and take their medication!

Founding Members: Today's accomplishments are built on the foundations laid by the early volunteers, and we are grateful for their efforts. TMS is where it is today because of the seeds that they planted in 1994 and in the early years. Below are some of the earliest members, but there have been many more champions who have served their fellow patients and families affected by Mastocytosis and Mast Cell Activation Disorders by volunteering for TMS. We salute you!

Past Board Members: THANK YOU to all of our past board members as they are our strong foundation for all the wonderful and exciting things happening now and in the future for TMS!

Linda Buchheit
Iris Dissinger
Ruth Sampson
Jane Clark
Juanita Anderson
Emily Tidball
Cindra Carey
Joan Passmore
Erin Cunia
Lisa Sterling
James McKee
Bill Richers
William Hingst
Bill Abbottsmith
Joyce McEntire
Kathy Favorite
Marcia Gordon
Diana Coleman
Michael Zorska
Emily Menard
Regina Rentz
Ethan Bordeaux
Celeste Thomason
Joseph Palk
Jessica Hobart
Margaret Thomas
Mishele Cunningham
Denise Baun
Candace VanAuken
Deborah Wallack
Lisa Kenny
Wanda Hermann
Janice Chiappone
Elizabeth Smith
Elizabeth Punsalan
Olive Clayson
Stephanie Shaw
Kristin Forest
Regis Park
Susan Manchester
Len Levenda
Jody Bachiman
Rachael Zinman
Michele Q. Kress
Sandra Frost

KOUNIS SYNDROME IN MAST CELL PATIENTS

Acute coronary syndromes can occur in allergic and anaphylactic reactions. One example, called Kounis Syndrome, is highly likely in patients with a wide variety of mast cell activation disorders and can affect patients of any age. The main triggers of Kounis syndrome are drugs, environmental exposures, and various pre-existing conditions. When patients such as mast cell disorder patients are on a protocol exposing them to many medications, the cascade leading to anaphylaxis and Kounis syndrome can be very rapid, with the heart and coronary arteries as the primary target.

Multiple mast cell mediators have direct action on coronary vessels and together result in hyperresponsiveness of mast cells, which can result in the Kounis syndrome cascade.

Please note: Coronary artery spasm induced by mast cell mediators may initiate Takotsubo Syndrome or stress induced cardiomyopathy during anaphylactic reactions.

Type1:Normal coronary arteries, no coronary disease, no pre-disposing conditions; acute allergic attacks resulting in coronary vasospasms without elevations in cardiac enzymes OR coronary vasospasm with myocardial infarction with elevation of cardiac enzymes and troponins

Treatment of the allergic episode can terminate the type 1 variant

- corticosteroids
- H1 and H2 blockers
- Vasodilators such as calcium channel blockers and nitrates can decrease hypersensitivity induced vasospasms

Type 2: Quiescient pre-existing atheromatous disease in whom acute allergic attacks can induce either vasospastic angina or plaque erosion, or rupture manifesting acute myocardial infarction

Treatment of acute coronary event comes first, then treat allergic attack

- -acute coronary event protocol
- -corticosteroids
- -H1 and H2 blockers

Type 3: Stent thrombosis with eosinophils and mast cells identified on pathology (Giemsa, hematoxylin-eosin stain)

Treatment of stent thrombosis with allergic attack

- -corticosteroids
- -H1 and H2 blockers
- -Mast cell stabilizers
- -Biopsy of thrombus stained for mast cells and eosinophils

CONSIDERATIONS

Nitroglycerin causes decreased blood pressure and increased heart rate. β blockers can exaggerate coronary vasospasms due to the unopposed actions of α-adrenergic receptors. Epinephrine is the drug of choice for anaphylaxis, however epinephrine can aggravate Kounis syndrome and worsen coronary vasospasm. If the patient is on β-blockers, glucagon administration should be considered along with epinephrine. Fentanyl is the opiate with the best profile for mast cell patients; administer with extreme caution.

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Thank you to the members of the TMS Medical Advisory Board for their review of this document.

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Emergency Care For Patients with **Mast Cell Disorders**

THE **MASTOCYTOSIS** SOCIETY, INC.

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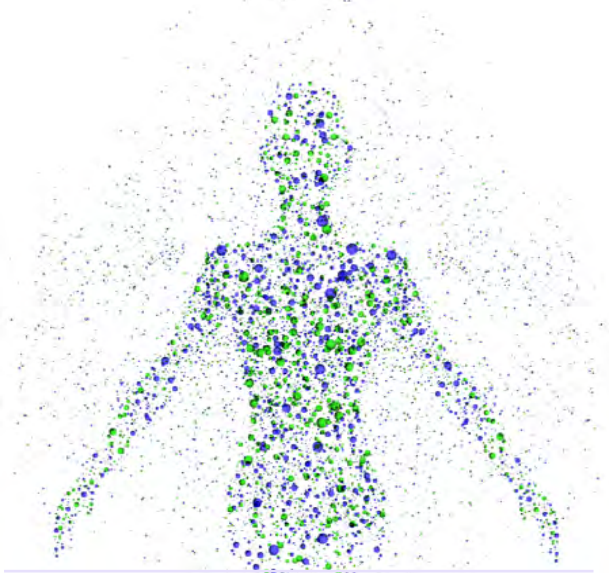


What Are Mast Cell Disorders

Mast cell disorders are characterized by abnormal mast cell proliferation/accumulation (mastocytosis), and/or activation (mastocytosis or mast cell activation syndrome (MCAS)), and affect both children and adults.

Mastocytosis can affect skin and internal organs such as the bone marrow, GI tract, liver and spleen, and most patients have either cutaneous or indolent systemic (benign) forms. Others, with more aggressive disease, may have associated hematologic disorders. Mast cell patients may have unpredictable symptoms that require anti-mediator therapy. Diagnosis of mastocytosis is confirmed by a bone marrow or skin biopsy. MCAS patients exhibit similar symptoms, and may or may not have increased measurable mast cell mediators for which we can currently test (serum tryptase, urinary N-methyl histamine, urinary prostaglandin D2 and 11-beta F2 alpha) during or immediately after an attack, and do respond to anti-mediator therapy.

Patients with mast cell disorders are more likely to experience life-threatening anaphylaxis than the general population. No correlation has been found between the signs and symptoms of anaphylaxis and serum tryptase levels or mast cell burden. The most common types of anaphylaxis are recurrent idiopathic anaphylaxis, hymenoptera anaphylaxis, or drug induced anaphylaxis. Anaphylaxis can also occur during anesthesia, indicating that appropriate perioperative management is critical.

ANAPHYLAXIS

Anaphylaxis is an acute, life-threatening, systemic reaction that results from the **sudden, rapid,** systemic release of mediators from mast cells and basophils.

Anaphylaxis symptoms present as new or worsening symptoms including:

- **Mouth:** itching, swelling of lips and/or tongue
- **Throat:** itching, tightness, closure, hoarseness
- **Skin:** itching, hives, redness, swelling, flushing
- **Gut:** nausea, vomiting, diarrhea, cramps
- **Lung:** shortness of breath, cough, wheeze
- **Heart:** weak pulse, dizziness, passing out

Only a few of these symptoms may be present. Although the diagnosis usually depends on the involvement of 2 organ systems, even if anaphylaxis presents with 1 organ system, epinephrine administration may be indicated. Anaphylaxis may present as an acute cardiac or respiratory event or with hypotension as the only manifestation of anaphylaxis.

Symptoms can be life-threatening! ACT FAST!

COMMON TRIGGERS OF MAST CELL REACTIONS AND ANAPHYLAXIS

Triggers are unique to each patient. If a patient tells you that a certain drug, substance or environmental factor is a mast cell trigger for them, believe the patient even if it does not seem plausible. Triggers can include, but are not limited to:

- Unknown trigger- Idiopathic anaphylaxis
- Hymenoptera venom and other venoms such as ant, snake, jellyfish and insect
- Medications including, but not limited to morphine and derivatives, IV Vancomycin, aspirin, NSAIDS; can be tolerated in some patients. Proceed with caution.
- Anesthesia drugs (succinylcholine, D-tubocurarine, gallamine, decamethonium) and radiocontrast dyes
- Food or beverage, including alcohol
- Emotional stress, anxiety and fatigue
- Physical stress, e.g., heat, cold, change in temperature
- Friction of skin lesions or vibration
- Exercise
- Latex, odors/perfumes

ANAPHYLAXIS GRADES

- **Grade I:** hives/rash, itching or swelling of mouth/throat
- **Grade II:** any of the above, plus- hypotension, tachycardia, dyspnea, presyncope, GI distress, including, but not limited to: pain, nausea, vomiting, diarrhea
- **Grade III:** any of the above, plus- profound hypotension, bradycardia or tachycardia, confusion, cardiovascular collapse, bronchospasm, hypoxia (SaO_2<92%)
- **Grade IV:** cardiac arrest

ANAPHYLAXIS TREATMENT IN A PRE-HOSPITAL SETTING: FOR PATIENTS

It is important to work with your primary mast cell physician to set up a signed home and emergency room protocol for anaphylactic/mast cell degranulation episodes. This protocol should include:

- When to take rescue medications, and what medications to take
- When to use IM epinephrine
- When to call 911 and go to the emergency room
- Assemble an emergency protocol packet, together with the names of doctors, care-givers, phone numbers, medications you take, diagnoses, allergies and mast cell protocol signed by your physician. Have multiple copies of these documents available for emergency personnel.
- If you go to the emergency department, request copies of all records including labs, x-rays, and treatments for your files and take these with you in the ambulance.
- If ER visit is required, go by ambulance if possible, and give the EMT all of your paperwork.
- If someone is driving you, recline as far back as you can or lie down in the back seat, have them pull up to the ER door, and alert emergency personnel that you are having anaphylaxis.

ANAPHYLAXIS TREATMENT IN A HOSPITAL SETTING: FOR PHYSICIANS

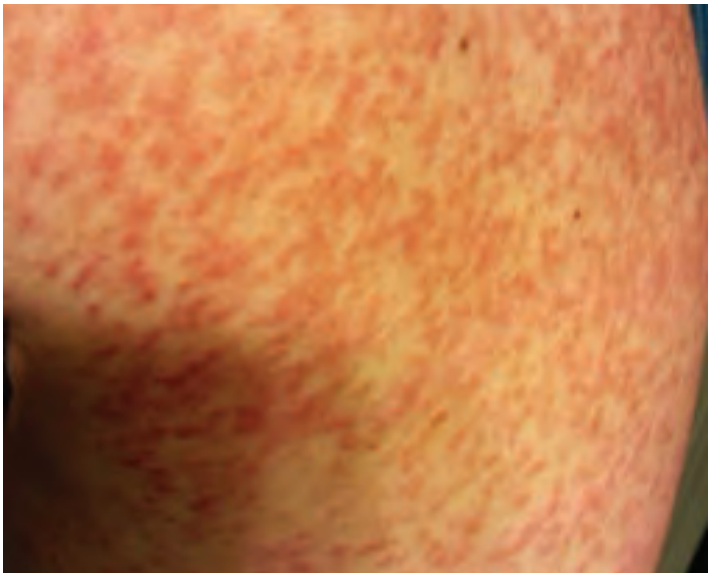
- Epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected. Although the diagnosis usually depends on the involvement of 2 organ systems, even if anaphylaxis presents with 1 organ system, such as the skin, epinephrine administration may be indicated.
- Anaphylaxis may present as an acute cardiac or respiratory event, with hypotension as the only manifestation.
- **Epinephrine given IM** (Vastus Lateralis muscle) is the drug of choice for treatment of anaphylaxis- concentration is 1:1000 (1mg/1ml) solution- 0.2mg-0.5mg for adults and 0.01ml/mg/kg for children- may repeat in 5-15 minutes, if needed.
- When giving epinephrine to a patient with a mast cell disorder who is experiencing anaphylaxis, care must be given to be sure the patient is not allergic to any of the ingredients in the epinephrine. Preservative free epinephrine may be preferable.
- "Because of the risk of potentially lethal arrhythmias, epinephrine should be administered IV only, in profoundly hypotensive patients or patients in cardio/respiratory arrest who have failed to respond to IV volume replacement and several injected doses of epinephrine."[13]
- Administer Oxygen
- Start large bore IV access
- Administer IV fluids if hypotensive.
- Consider inhaled bronchodilators if wheezing is present
- H1 and H2 Blockers as supportive therapy, preferably IV administration, including diphenhydramine as an H1 blocker, given 25mg-50mg, adults, and 1mg/kg, up to max 50mg dose in children; given very slow IV diluted in normal saline over 2-5 minutes. Hydroxyzine is an alternative H1 blocker in this situation. H2 antagonist, such as Famotidine, IV, should also be given.
- Corticosteroids may prevent prolonged anaphylaxis, although they may not have efficacy in the initial treatment of anaphylaxis.
- All mast cell patients must be monitored for biphasic reactions.

Visual Guide to Diagnosing Mastocytosis

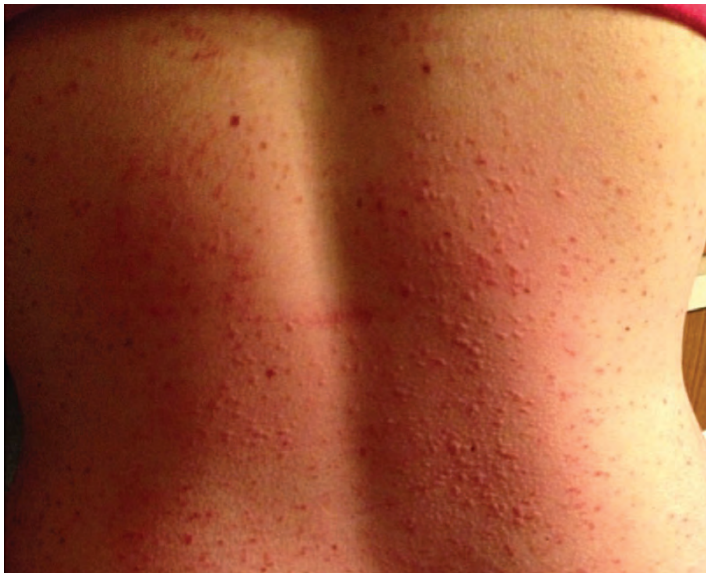
The following pages are a photo journal of examples of how mastocytosis can present. While cutaneous mastocytosis can include maculopapular cutaneous mastocytosis/urticaria pigmentosa (UP), telangiectasia macularis eruptiva perstans (TMEP), diffuse cutaneous mastocytosis (DCM), and solitary mastocytoma, skin manifestations can occur in mast cell activation syndrome (MCAS) and systemic mastocytosis (SM) patients as well.

Pediatric Mastocytosis

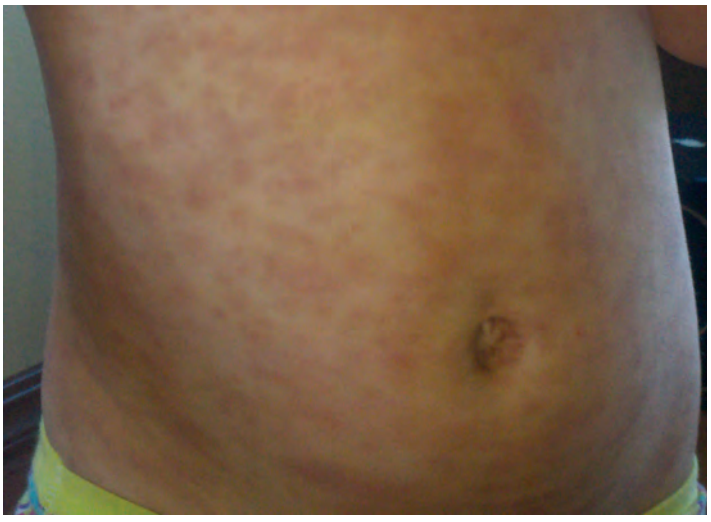
Most cases of pediatric mastocytosis fall into one of these categories and may or may not include symptoms of systemic mast cell activation as a result of mediators released from the skin (see Pediatric Mast Cell Disorders Fact Sheet in this issue). It should be noted that the term "UP" encompasses a variety of clinical manifestations. In children, some of these varieties will fade away, some will develop into indolent systemic mastocytosis and some will evolve into a newly described entity called well-differentiated systemic mastocytosis.



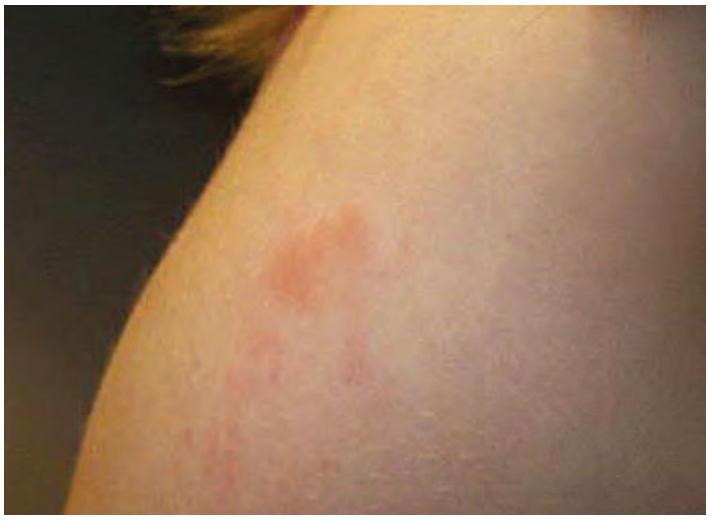
Pic. 1- Female adult with smoldering systemic mastocytosis and urticaria pigmentosa



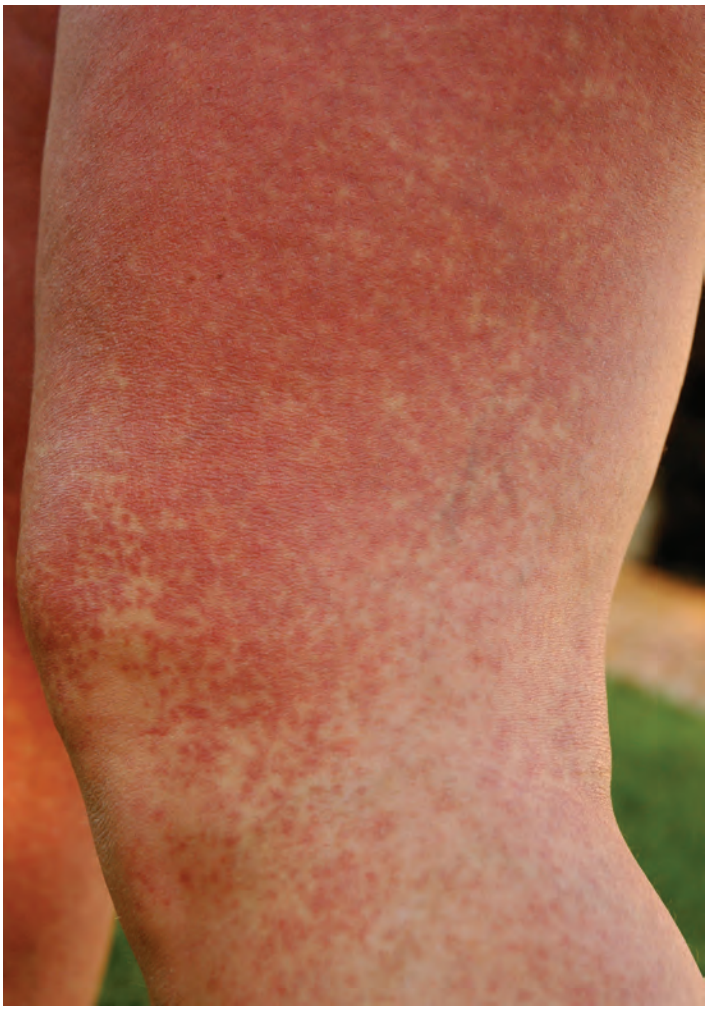
Pic. 2- Female adult athlete with hives and urticaria pigmentosa



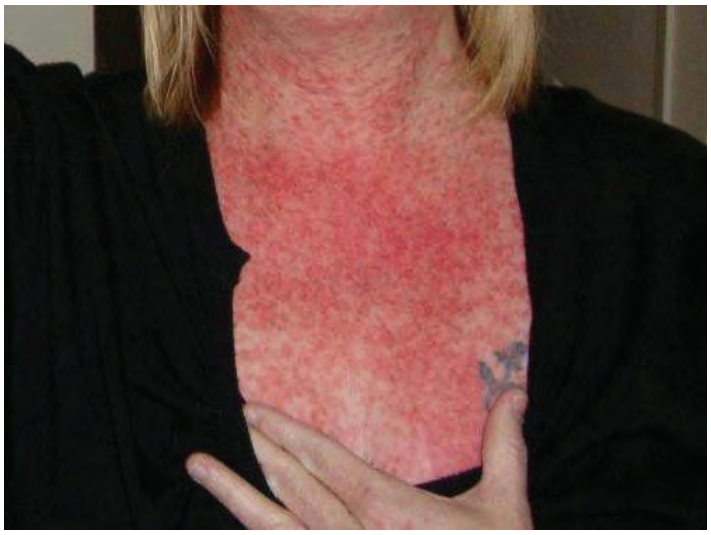
Pic. 3- Female child with systemic mastocytosis and urticaria pigmentosa



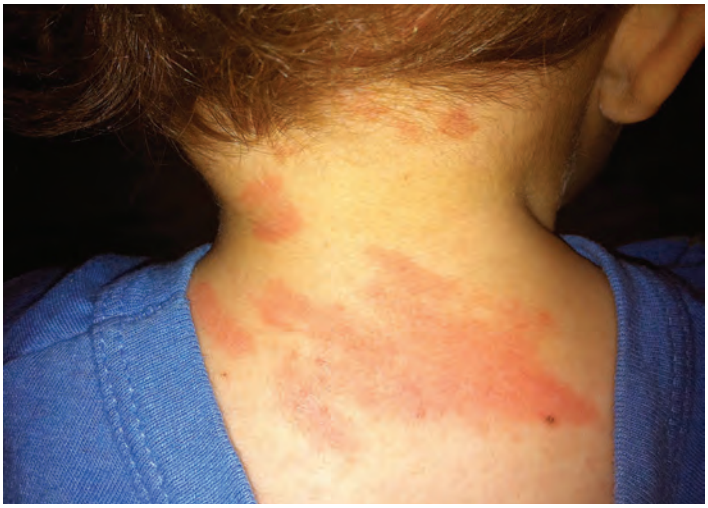
Pic. 4- Female child with mastocytoma on shoulder



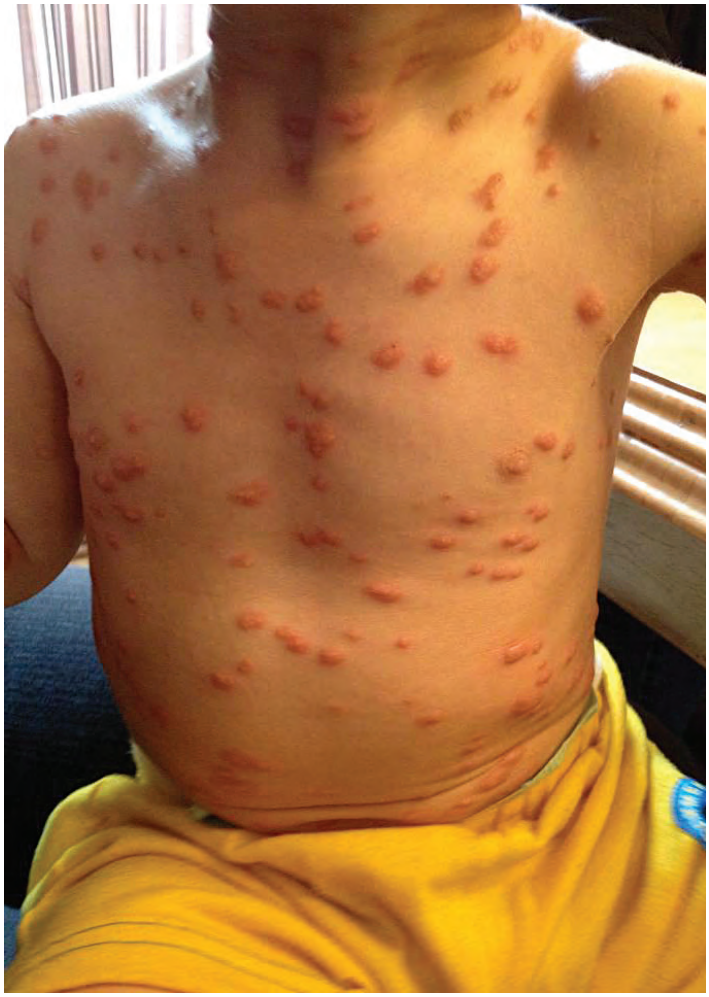
Pic. 5- Female adult with indolent systemic mastocytosis and confluent urticaria pigmentosa



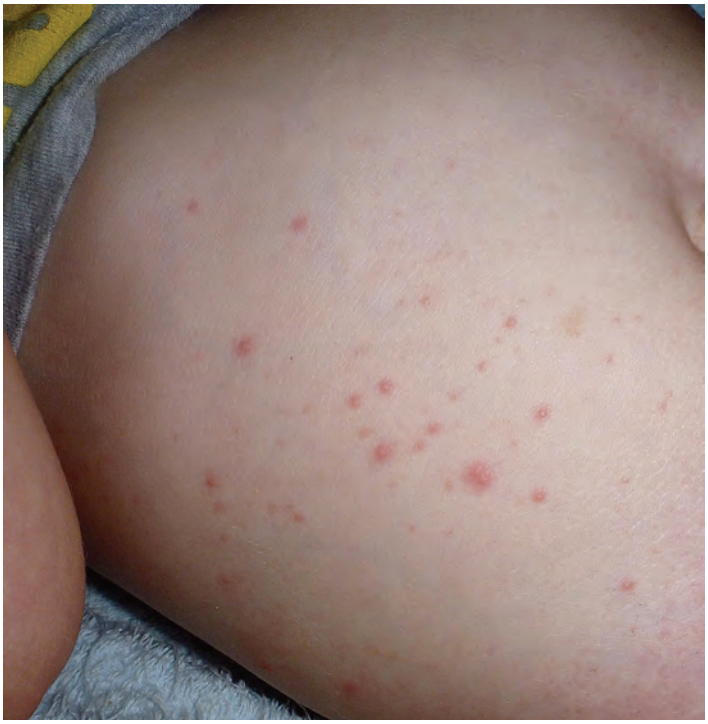
Pic. 7- Female adult with smoldering systemic mastocytosis, urticaria pigmentosa during a flare



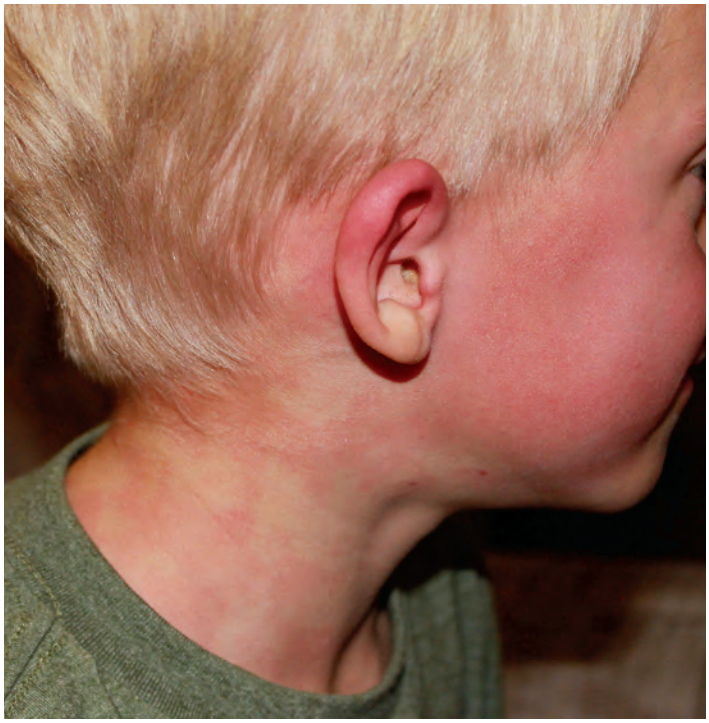
Pic. 6- Male child with systemic mastocytosis and mystery rashes



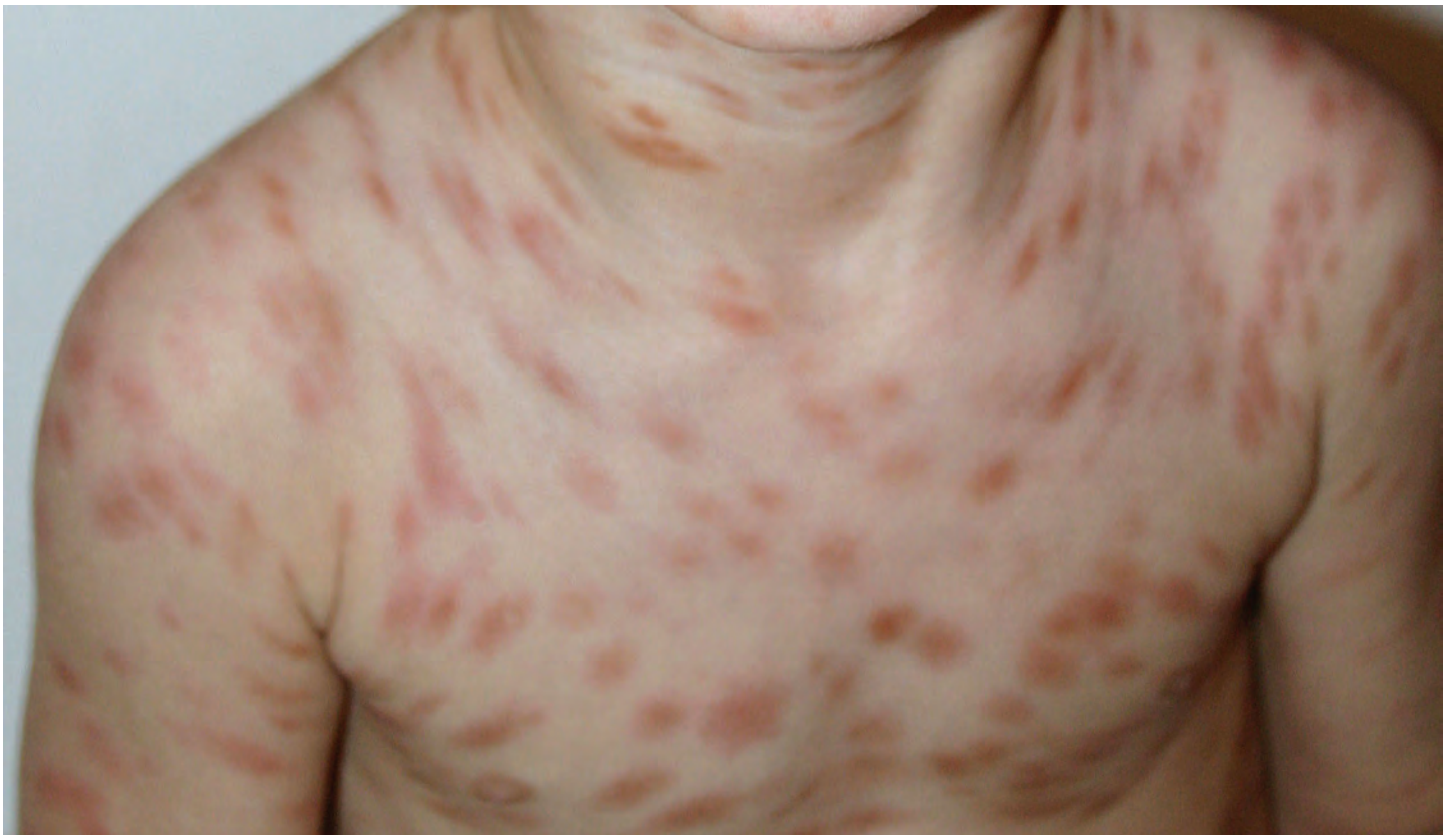
Pic. 8- Male child with urticaria pigmentosa



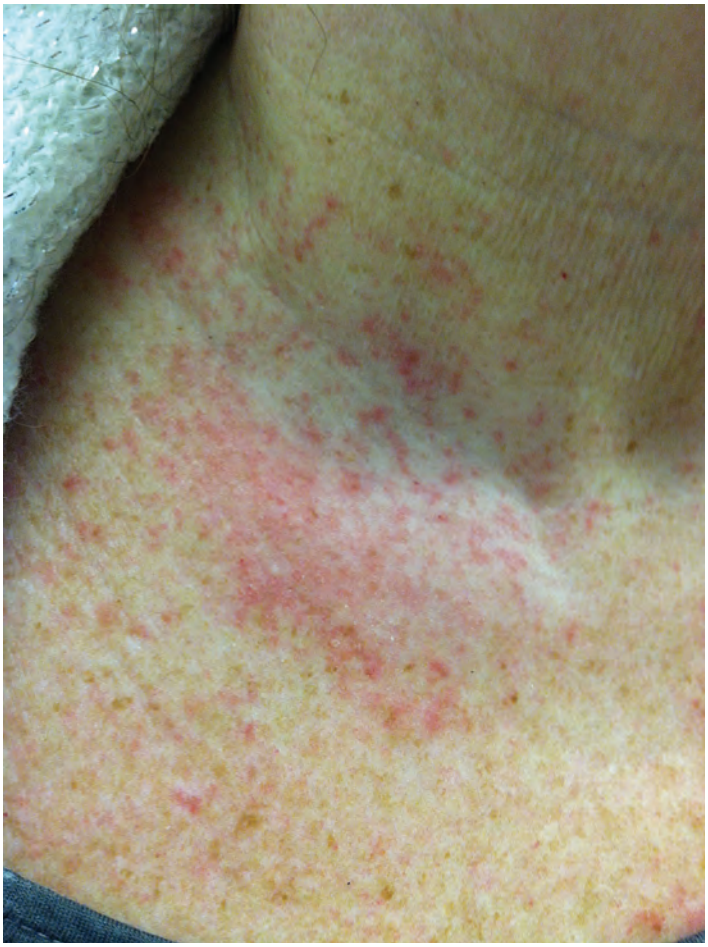
Pic. 9- Male child with systemic mastocytosis during flare causing blisters



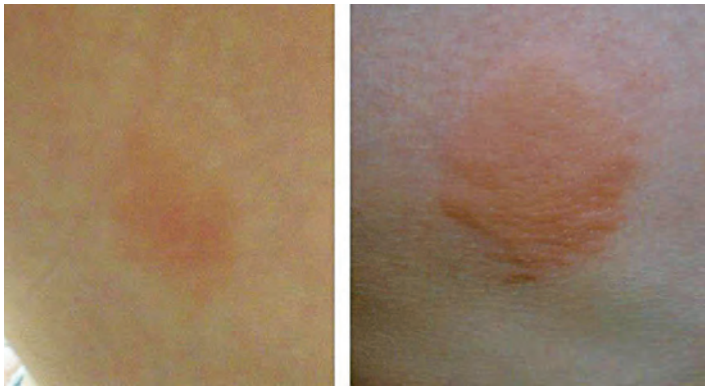
Pic. 10- Male child with mast cell activation syndrome, during flushing episode



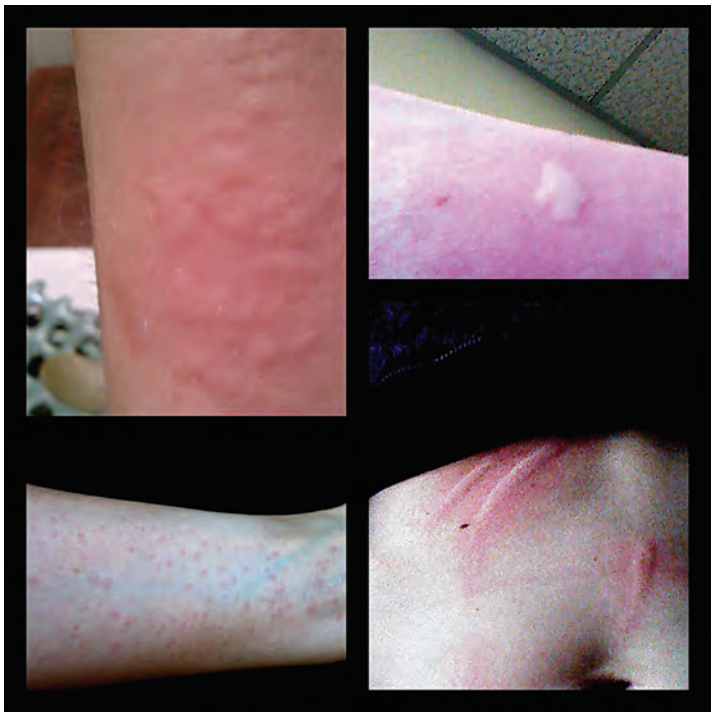
Pic. 11- Male child with urticaria pigmentosa



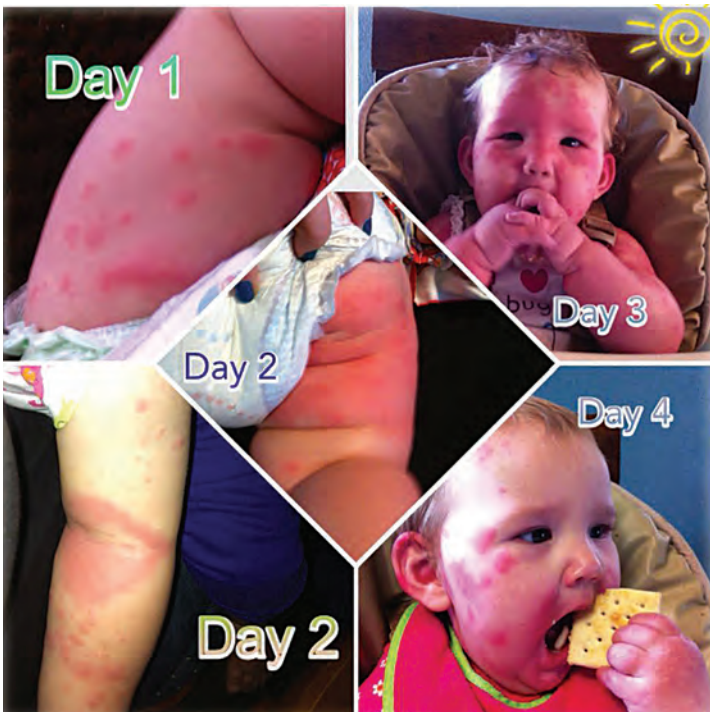
Pic. 12- Adult female with urticaria pigmentosa during a flare



Pic. 13- Solitary mastocytoma, normal and inflamed



Pic. 15- Female with idiopathic anaphylaxis and dermatographism



Pic. 14- Female child with urticaria pigmentosa

Thank You!!!

TMS would like to thank all the people who sent in images of mast cell disease. Education is one of our primary goals. Sharing these images with our members and medical professionals will help doctors better recognize mast cell disease.

MC ACTIVATION AND TRIGGERS

Mast cells release mediators, including tryptase, histamine, heparin, prostaglandins and leukotrienes, which result in the myriad symptoms patients can experience during mast cell activation/degranulation. Triggers of mediator release may include: heat; cold; temperature change; foods; medications; alcohol; friction; environmental, emotional, or physical stress; perfumes/odors; viral/bacterial/fungal infections; venoms; and fatigue. Some patients may experience reactions to certain medications, including but not limited to opiates, antibiotics and NSAIDs. Use with caution. Mast cell activation can occur along with, or independent of, any form of mastocytosis.

MC MEDIATOR SYMPTOMS AND THERAPY

Symptoms may include: flushing of the face, neck, and chest; headache; tachycardia and chest pain; abdominal pain, bloating, GERD, diarrhea, vomiting; rashes, including urticaria pigmentosa (UP), telangiectasia macularis eruptiva perstans (TMEP); bone/muscle pain, osteosclerosis, osteopenia, osteoporosis; itching, +/- rash; blood pressure instability; brain fog, cognitive dysfunction; anxiety/depression; lightheadedness, syncope; and anaphylaxis. Symptoms of mediator release are treated with H1 and H2 antihistamines, mast cell stabilizers, leukotriene inhibitors, and possibly aspirin (under ***direct supervision*** of a physician). All mast cell disease patients should carry two doses of injectable epinephrine unless otherwise contraindicated (Glucagon may need to be administered for patients on beta-blockers).

ADVANCED DISEASE CONSIDERATIONS

Advanced disease symptoms may include: anemia, thrombocytopenia, ascites, bone fractures, gastrointestinal abnormalities, and enlargement of the liver, spleen, and lymph nodes, which ultimately lead to organ failure and early death. Therapies of limited effectiveness exist for advanced SM, but promising new treatments are being developed. Prominent among these are tyrosine kinase inhibitors (TKIs) targeting the *KIT* kinase (e.g., midostaurin[6]). Imatinib is approved therapy for adult ASM patients lacking the KIT D816V mutation or if mutation status is unknown. Standard therapies for ASM are interferon and the chemotherapeutic agent cladribine, employed with antimediator therapy to reduce disease burden and control symptoms. In patients with SM-AHNMD, therapy selection usually depends on the associated disease, which is commonly more aggressive than the SM part. MCL requires a polychemotherapy approach.

REFFERENCES

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MISSION STATEMENT

The Mastocytosis Society, Inc. is a nonprofit organization dedicated to supporting patients affected by Mastocytosis or Mast Cell Activation Disorders as well as their families, caregivers, and physicians through research, education and advocacy.

ORGANIZATION AND SUPPORT

The Mastocytosis Society, Inc. (TMS) is a 501(c)3 organization lead by volunteers and guided by an expert medical advisory board. As defined in the mission statement, TMS provides support to patients, families, caregivers and physicians through research, education and advocacy. TMS welcomes mast cell disorder patients of all ages. Anyone affected by or interested in learning about mast cell disorders is encouraged to join.

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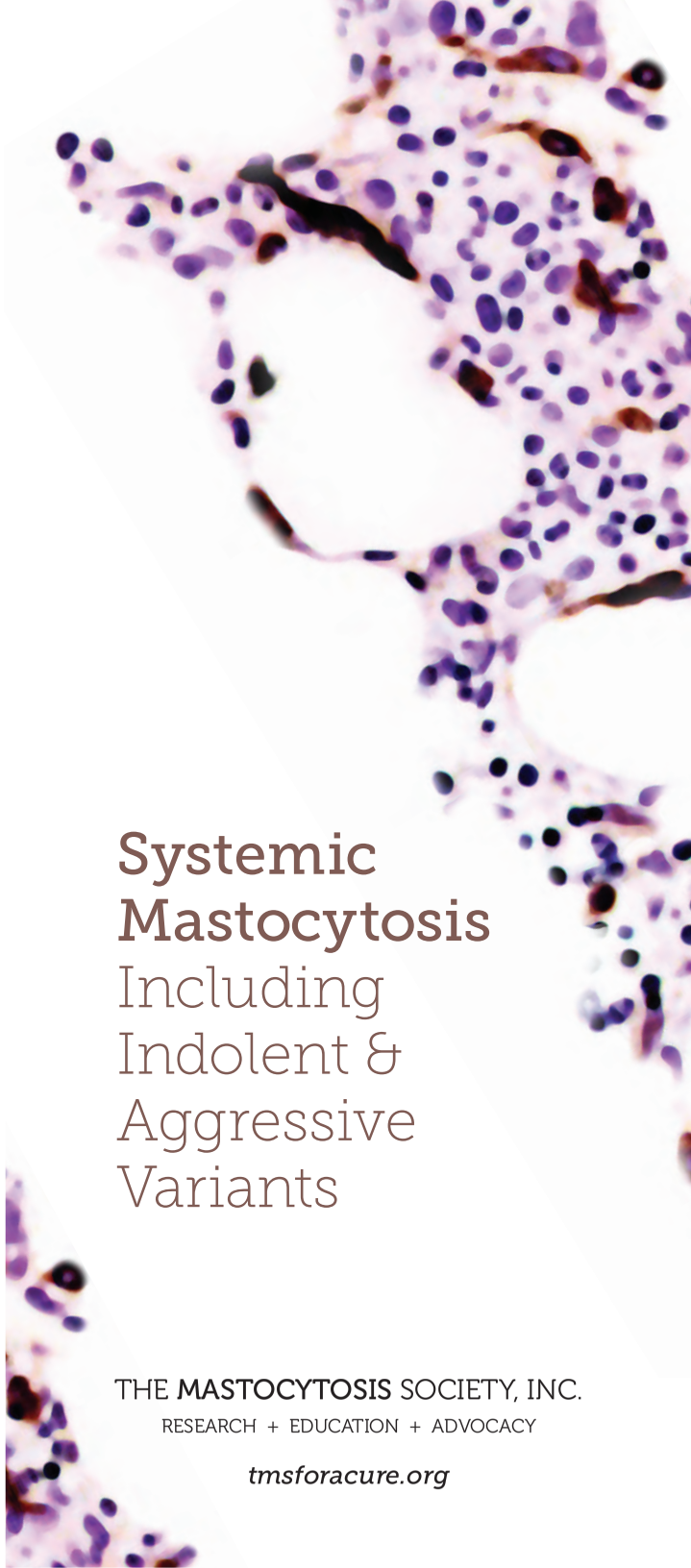
Mast Cell Disorders



Systemic Mastocytosis Including Indolent & Aggressive Variants

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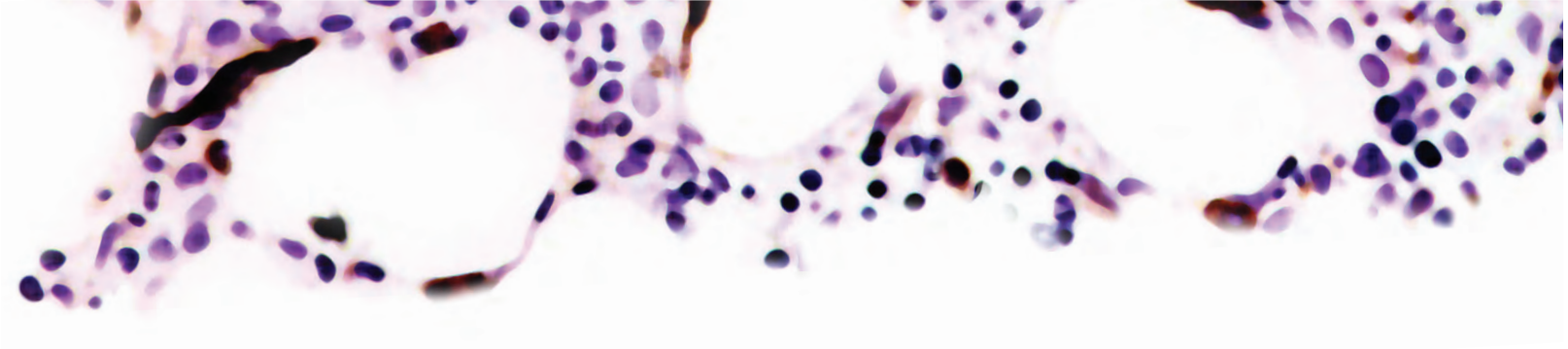
Systemic Mastocytosis Overview



Systemic mastocytosis (SM) consists of a group of rare, heterogeneous disorders involving growth and accumulation of abnormal mast cells (MCs) in one or multiple extracutaneous organ systems (**Table 1**).

TABLE 1. World Health Organization Diagnostic Criteria for Systemic Mastocytosis[1]

SM diagnosis requires at least one major and one minor criteria OR at least three minor criteria be fulfilled.
MAJOR CRITERION
Multifocal dense infiltrates of MCs (> 15 MCs in aggregates) are detected in sections of BM and/or other extracutaneous organ(s).
MINOR CRITERIA
> 25% of MCs in BM or other extracutaneous organ(s) display abnormal morphology (spindle shape typical).
Activating KIT mutation at codon 816 is found in extracutaneous organ(s).
MCs in BM, blood, or other extracutaneous organs express CD2 and/or CD25, plus normal MC markers.
Serum total tryptase is persistently > 20 ng/mL (not valid if there is an associated clonal myeloid disorder).

Standard technique can be used to obtain an iliac crest bone marrow (BM) biopsy and aspirate smear for diagnosis. Aspirated BM should be allocated for flow cytometry to assess for the presence of mast cells with aberrant phenotype (i.e., co-expression of CD25). Immunohistochemistry for KIT, MC tryptase, and CD25 should be performed on sections of the biopsy.

Patients who exhibit symptoms of mast cell mediator release who do not fulfill criteria for SM may have mast cell activation syndrome (MCAS), clonal or non-clonal.[5] Forms of mastocytosis include, but are not limited to, cutaneous mastocytosis (CM) and variants of systemic mastocytosis (**Table 2**). Pediatric mastocytosis is primarily a cutaneous disease (may include symptoms of mast cell activation), but 25-30% may go on to have some form of systemic disease in adulthood.

TABLE 2. Major Variants of Systemic Mastocytosis[1]

ISM (INDOLENT SYSTEMIC MASTOCYTOSIS)
WHO criteria for SM met, MC burden low, +/- skin lesions, no C findings, no evidence of AHNMD
Bone marrow mastocytosis: ISM with BM involvement, but no skin lesions
Smoldering SM: ISM, typically with skin lesions, with 2 or more B findings, but no C findings.
SM-AHNMD (SM WITH ASSOCIATED CLONAL HEMATOLOGIC NON MAST CELL LINEAGE DISEASE)*
Meets criteria for SM and also criteria for an AHNMD (MDS, MPN, MDS/MPN, AML), or other WHO-defined myeloid hematologic neoplasm, +/- skin lesions.
ASM (AGGRESSIVE SYSTEMIC MASTOCYTOSIS)
Meets criteria for SM with one or more C findings. No evidence of MCL, +/- skin lesions.
MCL (MAST CELL LEUKEMIA)
Meets criteria for SM. BM biopsy shows a diffuse infiltration, usually compact, by atypical, immature MCs. BM aspirate smears show 20% or more MCs. Typical MCL: MC comprise 10% or more of peripheral blood white cells. Aleukemic MCL: < 10% of peripheral blood white cells are MCs. Usually without skin lesions.

*A lymphoproliferative disorder or plasma cell dyscrasia may rarely be diagnosed with SM.

Thank you to Srdan Verstosek, MD, PhD, MD Anderson Cancer Center and Jason Hornick, MD, PhD,The Boston Center of Excellence for Mastocytosis at Brigham and Women's Hospital and Dana Farber Cancer Institute for their contributions to this brochure.TMS Research Committee.

PROGNOSIS

Most patients with SM have ISM. ISM patients have preserved organ function and their survival is comparable to that of the general population. Patients with smoldering SM may have an increased risk of developing disease transformation to aggressive forms of SM. Survival of patients with more *advanced* SM is significantly shorter than that of the overall population and is affected by disease subtype, with median survival of 41 months for patients with ASM, 24 months for SM-AHNMD, and 2 months for MCL.[3] Patients with ASM suffer debilitating symptoms and have signs of organ dysfunction (C-findings; **Table 3**). In patients with SM-AHNMD, prognosis can differ depending on the subgroup: in one study of patients with SM-AHNMD, the SM-myeloproliferative neoplasm, SM-chronic myelomonocytic leukemia, SM-myelodysplastic syndrome, and SM-acute leukemia subgroups were associated with median survivals of 31, 15, 13, and 11 months, respectively.[2]

TABLE 3. B and C Findings[1]

B FINDINGS
BM biopsy showing > 30% infiltration by MCs (focal, dense aggregates) and serum total tryptase level > 200 ng/mL
Myeloproliferation or signs of dysplasia in non–MC lineage(s), no prominent cytopenias; criteria for AHNMD not met
Hepatomegaly and/or splenomegaly on palpation without impairment of organ function and/or lymphadenopathy on palpation/imaging (> 2 cm)
C FINDINGS*
Cytopenia(s): ANC < 1 x 109/L, Hb < 10 g/dL, or platelets < 100 x 109/L
Hepatomegaly on palpation with impairment of liver function, ascites, and/or portal hypertension
Skeletal lesions: osteolyses and/or pathologic fractures
Palpable splenomegaly with hypersplenism
Malabsorption with weight loss from gastrointestinal tract MC infiltrates

* Must be attributable to the MC infiltrate.

Medical & Research Centers that Treat Patients with Mast Cell Diseases

Please note carefully any clarification of what each center specializes in. For example, some centers only treat patients with biopsy confirmed systemic mastocytosis, some centers only treat aggressive or malignant disease, some treat only adults or children, and many also treat mast cell activation syndromes/mast cell activation disorders (MCAS/MCAD). All centers listed can do the entire work-up including evaluation, physical exam, mediator testing and bone marrow biopsy with flow cytometry and appropriate stains for c-kit D816V mutation, tryptase, and expression of CD2 and CD25 antigen markers. Please be very clear when making your appointment to ask what you can expect to occur during your visit.

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Specialization: Biopsy proven only; including systemic mastocytosis (SM) only, aggressive SM and mast cell leukemia. Adults. Diagnostic, treatment, and research.

Colorado

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Professor, Division of Medical Oncology/Rella and Monroe Rifkin Endowed Chair
Email: William.Robinson@ucdenver.edu
Phone: 720-848-2869
Fax: 720-848-0704
Specialization: All mast cell related diseases including systemic mastocytosis (SM), aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL). Adults. Diagnostic (bone marrow biopsy can be arranged), treatment, and research.

Maryland

National Institutes of Health: National Institute of Allergy and Infectious Diseases

NIH, NIAID
Building 10, Room 11C207
10 Center Drive - MSC1881
Bethesda, MD 20892-1881

Contact: Dean D. Metcalfe, MD, Chief, Laboratory of Allergic Diseases

Email: dmetcalfe@niaid.nih.gov
Phone: 301-496-2165
Fax: 301-480-8384

Contact: Melody Carter, MD, Pediatrics

Email: mcarter@niaid.nih.gov

Specialization: Referrals only. Biopsy proven only; including systemic mastocytosis (SM) only, aggressive SM and mast cell leukemia. Adults and pediatric.

Diagnostic, treatment, and research. Bone marrow biopsies. Also adult idiopathic anaphylaxis.

Massachusetts

Center of Excellence for Mastocytosis (and Mast Cell Activation Disorders) at Brigham and Women's Hospital and Dana Farber Cancer Institute

Brigham and Women's Hospital
850 Boylston St., Suite 450
Chestnut Hill, MA 02467

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Email: daniel_deangelo@dfci.harvard.edu
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Address: DFCI, 450 Brookline Ave., Dana D1B30 Boston, MA 02215

Specialization: All mast cell related diseases including MCAS/MCAD. Adults and pediatric. Diagnostic, treatment, and research. Can arrange bone marrow biopsies.

Tufts University School of Medicine
136 Harrison Avenue
Boston, MA 02111

Contact: Theoharis Theoharides, MD, PhD, Professor of Pharm. and Internal Medicine

Email: theoharis.theoharides@Tufts.edu
Phone: 617-636-6866
Fax: 617-636-2456

Does not see patients in clinic

Michigan

Myeloproliferative Neoplasms and Systemic Mastocytosis Clinic

University of Michigan Comprehensive Cancer Center
1500 East Medical Center Drive
Ann Arbor, MI 48109

Contact: Marie Huong Nguyen, MD
Assistant Professor of Medicine (Hematology/Oncology)

Email: mariehtn@med.umich.edu
Phone (new patient coordinator): 734-232-2071
Phone (clinic): 734-647-8901
Fax: 734-232-1328

Specialization: Biopsy-proven only -- systemic mastocytosis (indolent, smoldering, aggressive SM), SM-AHNMD, and mast cell leukemia. Will perform diagnostic marrows for patients with elevated tryptase or biopsy-proven cutaneous disease.

Adults. Diagnostic, treatment, and research.

Minnesota

Mayo Clinic Center of Excellence for Mast Cell and Eosinophil Disorders
Mayo Clinic – Allergy Department
W15-B Mayo Clinic
200 SW 1st St.
Rochester, MN 55905

Co-Director: Joseph Butterfield, MD
Email: butterfield.joseph@mayo.edu

Co-Director: Catherine Weiler, MD, PhD
Email: weiler.catherine@mayo.edu

Phone: 507-284-9077
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Mayo Clinic – Hematology Department

Contact: Ayalew Tefferi, MD and

Animesh Pardanani M.B.B.S., PhD

Phone: (507) 284-5363

Specialization: All mast cell related diseases including MCAS/MCAD. Adults and pediatric. Diagnostic, bone marrow biopsy, treatment, and research.

University of Minnesota
Program for Mast Cell Diseases
Website: http://mastcell.umn.edu
Contact: Lawrence B. Afrin, MD (program director; sees adult mast cell disease patients)
Email: afrinl@umn.edu
Contact: Celalettin Ustun, MD (sees adult advanced/aggressive mastocytosis patients)
Email: custun@umn.edu
University of Minnesota
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Fax: 612-365-8101

Specialization: All mast cell-related diseases. Adult and pediatric patients. Diagnostic and treatment services and basic and clinical research.

Ohio

University of Cincinnati and

Bernstein Allergy Group and Research Center

8444 Winton Rd.
Cincinnati, OH 45231

Contact: Dr. Jonathan Bernstein, MD
Email: bernstja@ucmail.uc.edu

Phone: 513-931-0775
Fax: 513-981-0779

Specialization: All mast cell related diseases including MCAS/MCAD. Adults and pediatric. Diagnostic, treatment, and research. Can arrange bone marrow biopsies. Private family practice.

Oklahoma

University of Oklahoma,
College of Medicine
535 NW 9th St, Ste 325
Oklahoma City, OK 73102

Contact: Philip B. Miner Jr., MD
Clinical Professor of Medicine,
President and Medical Director,
Oklahoma Foundation for Digestive Research

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Texas

MD Anderson Cancer Center
1515 Holcombe Blvd, Unit 428
Houston, TX 77030

Contact: Srdan Verstovsek, MD, PhD, Associate Professor, Leukemia Department

Email: sverstov@mdanderson.org
Phone: 713-792-7305
Fax: 713-794-4297

Specialization: Systemic mastocytosis (SM) only, aggressive SM and mast cell leukemia. Adults. Diagnostic, treatment, and research.

Utah

The University of Utah School of Medicine, Department of Internal Medicine, Hematology Division

30 N 1900 E, Room 5C402
Salt Lake City, UT 84132

Contact: Michael Deininger, MD, PhD

Phone: 801-585-3229
Email: michael.deininger@hsc.utah.edu

Specialization: Bone marrow biopsy confirmed mastocytosis, aggressive disease and mast cell leukemia.

Virginia

Virginia Commonwealth University

P.O. Box 980263

1250 East Marshall St.
Richmond, VA 23298

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Internal Medicine: Rheumatology, Allergy, and Immunology

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Phone: 804-828-9685
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Specialization: All mast cell related diseases including MCAS/MCAD. Adults and pediatric. Diagnostic, treatment, and research. Can arrange bone marrow biopsies.

International (Active Centers)

Austria

Medical University of Vienna

Brazil

University of Sao Paulo, Sao Paulo

Denmark

Odense University Hospital

France

Association Française pour les Initiatives de Recherches sur le Mastocyte et les Mastocytoses (AFIRMM)

Germany

University of Berlin
University of Cologne
Technical University Munich Ludwig-Maximilians-University Munich

Greece

University Hospital of Athens - Attikon

Italy

University of Naples

Israel

Technion- Israel Institute of Technology, Haifa

The Netherlands

University Hospital Groningen

Poland

University of Gdansk

Portugal

University of Porto

Spain

Centro de Estudios de Mastocitosis de Castilla a Mancha (CLMast)

Sweden

Karolinska University Hospital, Stockholm

Switzerland

Kantonsspital Aarau, Aarau

Turkey

University of Istanbul

United Kingdom

Guy's and St. Thomas' Trust - London

Note: For additional current information on specialties and contacts within each European center visit: www.ecnm.net

Please note that the names of these centers and specialists are listed for informational purposes only. The Mastocytosis Society, Inc. is not responsible for any diagnostic evaluations, treatment or information provided as a result of visits or interactions with these medical professionals.

Medical Advisory Board

Contact Information

The Mastocytosis Society, Inc. is a nonprofit volunteer organization guided by a board of medical advisors who donate their time and expertise in support of the TMS mission. They have graciously agreed to act as a point of contact for other physicians and health care providers needing additional information about mastocytosis and mast cell activation disorders.

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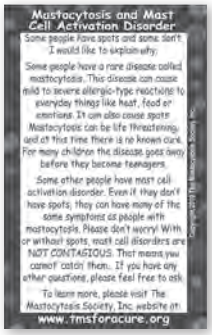
The Mastocytosis Society Printed Materials

Mastocytosis and mast cell activation disorders are complicated and not well-known diseases. To help educate and spread awareness, The Mastocytosis Society, Inc. (TMS) is pleased to offer informational material to physicians and patients.

Tri-fold Informational Brochures
Symptoms, diagnosis and treatment of mast cell disorders.

Infant Card



Generic Business Card

Card and Brochure Dimensions:
Spot Card, Generic Business .....2" x 3.5"
Informational Brochure, Tri-fold ..... 8.5" x 11"

Images not to scale

Ordering Information
TMS printed material will be provided free of charge to medical personnel, members and non-members. Donations are gladly accepted. If you require more than one of each item, please indicate quantity requested.

Name _____

Address_____

City _____

State _____ Zip _____

Phone _____

Email_____

Please indicate a quantity next to each item

Tri-fold Informational Brochures

____ Emergency Care For Mast Cell Disorder Patients

____ Systemic Mastocytosis Including Indolent & Aggressive Variants

____ Mastocytosis and Mast Cell Activation Disorders

Cards

____ Infant Card

____ Generic Business Cards

The Mastocytosis Society, Inc., PO Box 191752 Atlanta, GA 31119 | membership@tmsforacure.org

Mast Cell CONNECT
A mastocytosis patient registry

Mast Cell Connect, a Mastocytosis Patient Registry, Exceeds 100 Participants within First Month of Launch

Blueprint Medicines is pleased to announce that over 100 people from across the world have registered on Mast Cell Connect! Thank you to The Mastocytosis Society and to all participants who have signed up!

Visit MastCellConnect.org

About Mast Cell Connect's Sponsor

About Blueprint Medicines
Blueprint Medicines is a biopharmaceutical company developing a new investigational treatment for advanced systemic mastocytosis (SM). At Blueprint Medicines, we are motivated by one goal: to dramatically improve the lives of people with debilitating diseases. We are advancing three programs into clinical development for subsets of patients with SM, gastrointestinal stromal tumors, and hepatocellular carcinoma, as well as multiple programs in research and preclinical development. For more information, please visit www.blueprintmedicines.com.

About PatientCrossroads
PatientCrossroads is a leader in building web-based patient registries designed to advance research and connect patients with researchers, advocates and industry organizations working to understand or treat specific diseases and conditions. For more information, visit www.patientcrossroads.com.

Sponsored by

Powered by

Patient Crossroads™

Mast Cell Connect, an electronic patient registry designed to advance the understanding of mastocytosis, was launched in December 2015 by Blueprint Medicines in collaboration with Patient Crossroads. The goals for this registry are to further characterize mastocytosis epidemiology, improve the understanding of the natural history of the disease, and accelerate development of new therapies by increasing participation in clinical trials.

Blueprint Medicines is pleased to announce that over 100 people from across the world have registered on Mast Cell Connect! Thank you to The Mastocytosis Society and to all participants who have signed up!

Over 95% have completed the survey on Mast Cell Connect, and it is thrilling to see this level of engagement! One of the early insights we have learned is that when registry participants were asked what they are looking for in a new treatment, preventing mastocytosis-related symptoms was rated almost as important as improving the outlook for survival. The participants found depression and anxiety to be among the most debilitating and impactful factors they are dealing with in their day-to-day lives. This type of information can be useful not only when designing new therapies but also in current management of the disease.

By participating in the registry (www.mastcellconnect.org), individuals with mastocytosis will gain access to data and insights gleaned from other patients' responses that may be useful in better understanding their own disease. In addition, participants can sign up to be notified about clinical trials and other research studies that they may be eligible for based on information entered into the registry.

People with a diagnosis of mastocytosis, including systemic mastocytosis, cutaneous mastocytosis and subtypes of these diseases, are eligible to join. People with mast cell activation syndromes are not eligible to participate at this time. The registry protocol has been approved by a central institutional review board. Each participant's identity and data will be protected by standard identification measures, which take into account HIPAA privacy and security rules.

In conjunction with Mast Cell Connect, Blueprint Medicines launched the website Together with Systemic Mastocytosis, which is aimed at providing information to physicians and patients concerning this rare disease (www.systemicmastocytosis.com). Disease information, patient stories and expert interviews are designed to empower individuals with mastocytosis with knowledge of their disease. For those interested in sharing their story on the Together with Systemic Mastocytosis site or with questions concerning the registry, please feel free to contact

MEDICAL REFERENCE HIGHLIGHTS

Mastocytosis and Mast Cell Activation Syndromes

International Consensus Statements, Position Papers and WHO Criteria [1-11]

Reviews and Expert Opinions [12-35]

Laboratory Tests, Pathology, Immunohistology and Flow Cytometry [3, 29, 31, 33, 34, 36-41]

Perioperative Management/Pre-Medication for Dental Work, Diagnostic Testing or Surgical Procedures [2, 28, 42-44]

Therapy [27, 28, 31, 45, 46]

The Mastocytosis Society Survey on Mast Cell Disorders [47]

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2. Bonadonna P, Pagani M, Aberer W, Bilo MB, Brockow K, Oude Elberink H, et al. Drug hypersensitivity in clonal mast cell disorders: ENDA/EAACI position paper. Allergy. 2015 Jul;70(7):755-63.
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Members who have given beyond their annual $35 dues when renewing their membership or starting a new membership are considered supporting members. This does not include those who made major contributions to other initiatives such as the Walk-A-thon or TMS Conference, but rather designates different levels of donations made at the time of membership dues.

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2015 Walk A Thon Total	34,780.75
Sarah Gittleman Memorial Fund	9,199.00
Wyatt Warrior Walk/Fundraiser	34,831.21
Gary Meyer Fundraiser	7,636.45
Research Contributions	10,040.20
Blue Print Medicines	10,000.00

Thank You!

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The Mastocytosis Society, Inc

PO Box 191752 Atlanta, GA 31119

Membership Form

Applicant Information (please type or print):

Name: _____ Child Member's Name: _____

Address: _____

City: _____ State: _____ Zip: _____ Country: _____

Phone: _____ E-Mail: _____

Member: _____ Relative _____ Spouse _____ Child _____ Caregiver _____ Friend _____

Membership Type: New ($35)_____ Renewal ($35) _____ Supporting Member _____

Supporting Members are listed in *The Mastocytosis Chronicles* and will receive a thank you gift.

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Silver Member ($150) _____
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Would you like to double your annual dues to include a donation to the *Angel Fund* for individuals with a mast cell disorder who are unable to pay the annual membership fee of $35 Yes No _____

Total amount to be paid :_____(i.e., $35 dues plus one (1) Angel Fund donation of $35 is $70 total)

Check enclosed_____ Money Order_____ Paid Online_____

Make check or money order payable to **The Mastocytosis Society,** and send to:
The Mastocytosis Society, c/o Treasurer P.O. Box 191752 Atlanta, GA 31119

ANGEL FUND WAIVERS

Patients who are unable to afford to pay dues at this time can have their dues waived through the "Angel Fund Program". This Program was established to assist Patients with a Mast Cell Disorder to pay their dues. If you would like your dues paid through the "Angel Program" due to financial hardship, please send a letter requesting an Angel Fund Waiver (to the address above) or an email to membership@tmsforacure.org.

Those who are interested in learning more about the disease who are not patients but would like their membership fee waived because of financial difficulties may send a letter to the Board of Directors (to the address above) or an email to tmsbod@tmsforacure.org requesting a waiver which may be approved through another fund.

Preferred Chronicle distribution method: E-mail ____ U.S. Mail _____ International Mail _____
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THE MASTOCYTOSIS SOCIETY

Mast Cell Disorders

Membership Application Angel Fund Waiver Form

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Name: _____ Child Member's Name:_____

Address: _____

City: _____State:_____Zip:_____Country:_____

Phone: _____ E-Mail:_____

Membership Type: New _____Renewal _____

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THE MASTOCYTOSIS SOCIETY

Mast Cell Disorders

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