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, with 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 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. Since then there have been many more champions who have served their fellow patients and families affected by Mastocytosis and Mast Cell Activation Diseases 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!
The Mastocytosis Chronicles

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American Initiative in Mast Cell Diseases (AIM)

By Susan Jennings, PhD, and Valerie Slee, RN, BSN – September 2019

Since 2014, The Mastocytosis Society, Inc. (TMS) has hosted small ancillary Mast Cell Disorder Challenges meetings during specialty medical conferences. The objectives of these meetings have been to bring together specialist physicians, drug company representatives and members of the TMS Research Committee to identify primary challenges facing the mast cell disease community in the United States and to explore possible actions to address those challenges. A key conclusion from our initial meetings was that the establishment of a US network for mast cell diseases would be extremely helpful in overcoming many of the challenges faced by our disease community. During these meetings, our US physicians have received significant support from many international mast cell disease specialists, who have shared their experiences of forming networks in their own countries and more broadly in Europe. TMS has collaborated with a committee established for the formation of an American network, under the direction of Jason Gotlib, MD, MS, and Cem Akin, MD, PhD, as Co-Chairs. In May 2019, the TMS Patient/Caregiver Conference was paired with the inaugural investigator meeting of the American Initiative in Mast Cell Diseases (AIM). AIM will be a network of centers established across North, Central and South America, with a goal of excellence in patient diagnosis and treatment, and collaboration on research initiatives. AIM will collaborate closely with the European Competence Network on Mastocytosis (ECNM), which has centers established throughout Europe.

Please see www.aimcd.net for more information on the American Initiative in Mast Cell Diseases.
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Special Edition For Health Care Professionals

The special edition of The Mastocytosis Chronicles has been published specifically for physicians and health care professionals since 2007. This edition contains diagnostic and treatment information for mastocytosis and mast cell activation diseases, locations of mast cell disease treatment centers, physician contact information, documentation of research articles, and other pertinent information. For additional information visit www.tmsforacure.org.

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We thank each of these doctors for their time, caring, and expertise.

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

TMS is proud to be a Lay Organization member of The American Academy of Allergy Asthma and Immunology (AAAAI)

Our Mission

The Mastocytosis Society, Inc. is dedicated to providing multi-faceted support to patients, families and medical professionals in our community and to leading the advancement of knowledge and research in mast cell diseases through education, advocacy and collaboration.
What are Mast Cells?

Mast cells (MC) are immune system cells that live in the bone marrow and in body tissues, internal and external, such as the gastrointestinal tract, the lining of the airway, and the skin. Everyone has mast cells in their body, and they play many complex and critical roles in keeping us healthy. The positive roles that they play include protecting us from infection, and helping our body by participating in the inflammatory process. However, mast cells are also involved in allergic reactions, from the tiny swelling that appears after a mosquito bite to a life threatening, full-blown anaphylaxis.

Mast cells have within them small sacs, or granules, surrounded by membranes (Figure 1). The sacs contain many different kinds of substances called mediators, which participate in all of the roles above, including allergic response and anaphylaxis. The mediators are selectively released when there is an allergic or mast cell based reaction.¹

There is a difference between someone who is healthy, with mast cells that are functioning normally, and someone with a mast cell disease, whose mast cells may be activating inappropriately, sometimes in response to triggers, or may also be proliferating and accumulating in organ tissues.

What are Mast Cell Diseases?

Mast cell diseases are caused by the proliferation and accumulation of genetically altered mast cells and/or the inappropriate release of mast cell mediators, creating symptoms in multiple organ systems.² The three major forms of mast cell diseases are mastocytosis, mast cell activation syndromes (MCAS), and hereditary alpha tryptasemia (HaT). HaT is caused by a duplication or triplication of the alpha-tryptase gene.²a Mast cell diseases can cause tremendous suffering and disability due to symptomatology from recurrent mast cell mediator release, and/or symptoms arising from infiltration and accumulation of mast cells in major organ systems. In addition, those suffering from HaT may experience additional symptoms from

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*Figure 1. Mast cell (electron micrograph)*

Mast cell granule (sac) which contains mediators

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Continued on page 6
Overview, Definitions, Diagnosis and Classification

Continued from page 5

dysautonomia and connective tissue disease. Although systemic mastocytosis is a rare disease,2 those suffering with MCAS and/or HaT have recently been increasingly recognized and diagnosed. As a result, patients with MCAS and/or HaT appear to represent a growing proportion of the mast cell disease patient population.4, 5 It is important to note that the process of mast cell activation can occur in anyone, even without a mast cell disease, as well as in patients with mastocytosis, MCAS, and HaT.6

MASTOCYTOSIS

Definition

Mastocytosis has been defined in the literature as an abnormal accumulation of mast cells in one or more organ systems. Previously classified by the World Health Organization (WHO) as a myeloproliferative neoplasm, mastocytosis is now classified in its own category under myeloid neoplasms.7 Broadly separated into three categories – cutaneous mastocytosis (CM), systemic mastocytosis (SM) and mast cell sarcoma – these diseases occur 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.8-10 In pediatric mastocytosis, symptoms of mast cell mediator release may occur systemically as a result of mast cell mediators released from skin lesions.10 This, however, does not necessarily indicate systemic disease. The incidence of systemic pediatric disease was previously unknown, but systemic forms have now been proven to exist in some children.8-10 The majority of adult patients are diagnosed with systemic disease. Skin involvement, typically maculopapular cutaneous mastocytosis/urticaria pigmentosa, is common in adult patients and can provide an important clue to accurate diagnosis.11, 12

Diagnosis and Classification13-17

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 WHO has established criteria for diagnosing SM, summarized18 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 816V 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 SM-AHN-type disease.)

Abbreviation Key:
KIT: Mast cell growth receptor/tyrosine kinase receptor
MC(s): Mast cells;
SM-AHN: Systemic mastocytosis with associated hematologic neoplasm.

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.
**MAST CELL ACTIVATION SYNDROMES**

**Definition**

Existence of a subset of mast cell disease patients who experience episodes of mast cell activation without detectable evidence of a proliferative mast cell disease was postulated over 20 years ago.\(^{19, 20}\) Over the last two decades, with development of improved methodology for identification of abnormal mast cells,\(^{21-24}\) it became apparent that there were patients who exhibited symptoms of mast cell mediator release who did not fulfill the criteria for SM.\(^{25, 26}\) Thus began the evolution of discussions about other forms of mast cell diseases, both clonal and nonclonal, which became known as Mast Cell Activation Syndromes (MCAS).\(^{6, 27, 28}\)

**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 diseases,\(^{6}\) where mast cell activation plays a prominent role.

Mediators produced by mast cells have a considerable effect on specific symptomatology. Symptoms, including, but not limited to flushing, pruritis (itching), urticaria (hives), headache, gastrointestinal symptoms (including diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux), and hypotension (low blood pressure), 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 recur, or are chronic, are found not to be caused by any other condition or disorder other than mast cell activation, and require treatment or therapy.\(^{6, 28}\)

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.\(^{6, 28-30}\) The consensus article provides a method for calculating the required minimum rise in serum tryptase.\(^{6}\) After a reaction, a level of serum tryptase that is a minimum of 20% above the basal serum tryptase level, plus 2 ng/ml, will meet the second criterion listed above for a mast cell activation event. 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, 11\(\beta\)-prostaglandin-F\(_2\)\(_\alpha\) (24-hour or spot 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.\(^{6}\)

Finally, the third co-criterion requires a response (based on response criteria\(^{15}\)) to medications that inhibit the action of histamine.\(^{9}\) In addition, in those with typical mast cell activation symptoms, 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.\(^{6, 28}\)

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References


<table>
<thead>
<tr>
<th>Mast cell types</th>
<th>Morphology</th>
<th>Types of disease</th>
</tr>
</thead>
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<tr>
<td>Normal/reactive</td>
<td>Round, well-granulated, with granules that fill the cytoplasm and obscure the nucleus; round to oval nucleus</td>
<td>Normal marrow, mast cell hyperplasia, well differentiated SM</td>
</tr>
<tr>
<td>Atypical type I (spindle shaped)</td>
<td>Hypogranular, enlarged, with cytoplasmic projections</td>
<td>Indolent SM, ASM, SM-AHN</td>
</tr>
<tr>
<td>Atypical type II (promastocyte)</td>
<td>Enlarged and round, hypogranular; indented bilobed nuclei</td>
<td>Mast cell leukemia, myelomastocytic leukemia</td>
</tr>
<tr>
<td>Metachromatic blast (immature)</td>
<td>Hypogranular with a few large metachromatic granules; high nuclear-to-cytoplasm ratio; smooth chromatin in nuclei</td>
<td>Mast cell leukemia, myelomastocytic leukemia</td>
</tr>
</tbody>
</table>

SM: Systemic mastocytosis  
ASM: Aggressive systemic mastocytosis  
SM-AHN: Systemic mastocytosis with an associated hematologic neoplasm [previously referred to as SM-AHNMD (systemic mastocytosis with an associated (clonal) hematologic non-mast cell lineage disease)]  

**Reference**  
Cutaneous Mastocytosis Variants

An international consensus task force of mast cell disease specialists has recently proposed updates to the diagnostic criteria and classification for cutaneous disease.1 Typical skin lesions found in mastocytosis, along with a positive Darier’s sign (see below), is the major criterion for diagnosing skin involvement in patients with mastocytosis. The two minor criteria are identified via skin lesion biopsy: increased mast cell numbers and the presence of an (activating) KIT mutation.1, 2 Cutaneous mastocytosis (CM) includes three variants: maculopapular cutaneous mastocytosis (MPCM), which includes urticaria pigmentosa (UP) and telangiectasia macularis eruptiva perstans (TMEP), diffuse cutaneous mastocytosis (DCM), and cutaneous mastocytoma.1 The taskforce recommends that telangiectasia macularis eruptiva perstans (TMEP) be removed as a separate category because, although some adult patients may have telangiectatic lesions on their chest, shoulders, neck and back, they may also demonstrate maculopapular lesions in other places, therefore fulfilling criteria for MPCM.

Most cases of pediatric mastocytosis fall into one of the above categories and may or may not include symptoms of systemic mast cell activation, including anaphylaxis, as a result of mediators released from the skin.3, 4 Pediatric CM encompasses a variety of clinical manifestations. In children, some forms of CM will spontaneously resolve, some will go on to be diagnosed as indolent systemic mastocytosis (ISM), with a smaller percentage identified as well-differentiated systemic mastocytosis (WDSM).5

In most adults with skin lesions typical for mastocytosis (in particular, the maculopapular type), systemic disease will ultimately be found, leading to a diagnosis of systemic mastocytosis, usually in an indolent form (indolent systemic mastocytosis).1, 8

Definitions1, 7

Darier’s sign is an important diagnostic finding of patients with mastocytosis. It can be elicited by stroking an existing CM lesion with a wooden tongue depressor, approximately 5 times with moderate pressure. Within a few minutes, a wheal and flare reaction of the lesion will be seen. A positive Darier’s sign is usually seen in pediatric patients, but not always in adults. It may be decreased by treatment with antihistamines. If the testing procedure for Darier’s sign is not done properly, false positives or false negatives may result. Darier’s sign is to be applied to the evaluation of fixed cutaneous lesions except in the case of a pediatric patient with cutaneous mastocytoma or nodular lesions. Testing for Darier’s sign may provoke a systemic reaction and should either be performed with the greatest of caution or avoided.

Dermatographism is a skin reaction characterized by a wheal and flare response when normal skin, not affected by skin lesions, is stroked with a tongue depressor, finger nails or other instrument. The nick-name for dermatographism is skin writing disease.

A macule is a lesion that is flat and even with the surrounding skin, identified by a change in color compared to the surrounding skin.

A papule is a small bump or elevated lesion, up to 1 cm in diameter, containing no visible fluid.

A nodule is a growth of abnormal tissue just below the skin.

A bulla is a large blister filled with fluid.

Telangiectasia is a vascular lesion formed by dilatation of a group of small blood vessels.

VARIANTS OF CUTANEOUS MASTOCYTOSIS

Maculopapular Cutaneous Mastocytosis (MPCM)/Urticaria Pigmentosa (UP)1

- May be seen in infants, children or adults
- Adults presenting with maculopapular lesions have a very high likelihood of systemic disease, most frequently indolent systemic mastocytosis (ISM)
- Rarely, an adult presents with maculopapular lesions who does not have systemic disease, and has a diagnosis of MPCM
- 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 pruritis5
• Encompasses several clinical entities with different outcomes, including: pitted melanotic macules, reddish brown telangiectatic macules, lightly pigmented papules, brownish papules, and small nodules
• This group is divided into two sub-variants
  ° Monomorphic variant
    - Mostly seen in adults and in a small subgroup of children
    - Small maculopapular lesions, similar in shape, size and color
    - Adults most typically express the *KIT* D816V mutation in exon 17 of the *KIT* gene
    - In adults, thigh, axilla, trunk, extremities and neck may be involved
    - 95% of adults diagnosed with ISM, 50% with advanced systemic mastocytosis [systemic mastocytosis with an associated hematologic neoplasm (SM-AHN, formerly SM-AHMND) or aggressive systemic mastocytosis (ASM)] and less than 50 % of mast cell leukemia patients exhibit this variant
    - Children presenting with this form may have increased serum tryptase and a tendency toward systemic disease that persists into adulthood
    - The type of lesions can vary during the course of the disease, i.e., nodules during infancy may turn into plaques at age 6
  ° Polymorphic variant
    - Mostly seen in children
    - Can be macular, plaque or nodular, with lesions of variable shape, color and size
    - Although children typically express mutations in exon 8, 9, 11 or 17 of the *KIT* gene, *KIT* mutations may be negative
    - Usually involving head, neck and extremities
    - May involve blistering upon irritation until 3 years of age
    - Prognosis is favorable with regression of disease in adolescence or young adulthood

**Cutaneous Mastocytoma**

• Usually present at birth
• Elevated lesion(s) (up to a total of three lesions) which usually resolves during childhood
• Four cutaneous mastocytomas or more become a diagnosis of MPCM
• Multiple mastocytomas may evolve into adult WDSM

**Diffuse Cutaneous Mastocytosis (DCM)**

• Skin thickened, hyperpigmented and diffusely infiltrated
• Can involve up to 100% of the skin with the trunk, head and scalp heavily affected
• Can appear at birth or early infancy; may persist into adulthood, possibly as well differentiated systemic mastocytosis (WDSM)
• Blisters, some of which are hemorrhagic, and bullae may be 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 WDSM

**References**

Systemic Mastocytosis Variants

Systemic mastocytosis (SM) consists of a group of rare, heterogeneous diseases involving growth and accumulation of abnormal mast cells (MC) in one or multiple extracutaneous (non-skin) 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.1,5

Recent Updates in Diagnosis

A new diagnostic algorithm has been proposed by the European Competence Network on Mastocytosis for evaluating patients with suspected mastocytosis.6 Recommendations for KIT mutation analysis, including in peripheral blood, have also been recently published.7

Table 1. Major Variants of Systemic Mastocytosis6

<table>
<thead>
<tr>
<th>ISM (Indolent systemic mastocytosis)</th>
<th>WHO criteria for SM met, MC burden low, +/- skin lesions, no C findings, no evidence of AHN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bone marrow mastocytosis: ISM variant with BM involvement, but no skin lesions</td>
<td></td>
</tr>
<tr>
<td>SSM (Smoldering systemic mastocytosis)</td>
<td>WHO criteria for SM met, typically with skin lesions, with 2 or more B findings, but no C findings.</td>
</tr>
</tbody>
</table>

Advanced Disease Variants

SM-AHN (SM with an associated hematologic neoplasm, formerly SM-AHNMD)

Meets criteria for SM and also criteria for an AHN (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.

*SM-AHN is the recently updated term from the 2016 WHO classification of mastocytosis; a lymphoproliferative disorder or plasma cell dyscrasia may rarely be diagnosed with SM.

Table 2. B and C Findings

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

*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). 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 disease. Treatment usually includes mediator-targeting drugs, including antihistamines, but does not usually require cytoreductive agents, although there are exceptions.

Isolated bone marrow mastocytosis (BMM) is a variant of indolent SM. BMM is characterized by the absence of skin lesions, lack of multi-organ involvement, and an increased incidence of anaphylaxis.

Well differentiated SM (WDSM) first described in 2004, is reported in the literature as a rare variant that fulfills the major criterion for SM and continues to be studied by researchers. WDSM is distinguished from pediatric cutaneous mastocytosis by its inclusion in the systemic category, despite that 91% of patients with WDSM have childhood onset of disease, with familial involvement in 39%. There is a heterogeneous presentation of lesions, maculopapular, nodular and diffuse cutaneous, that may involve a large percentage of the skin. Severe mast cell symptoms can occur and the variant may persist into adulthood in a low percentage of cases. The mast cells often do not express CD25 or CD2 that are part of the minor World Health Organization (WHO) criterion for SM, but may have CD30. Also, roughly 90% of WDSM patients don’t have the KIT D816V or other exon 17 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. Baseline serum tryptase levels

Continued on page 14

91% of patients with WDSM have childhood onset of disease, with familial involvement in 39%
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 KIT D816V mutation, which causes resistance to imatinib.18

**SMOLDERING SYSTEMIC MASTOCYTOSIS**

Smoldering systemic mastocytosis (SSM) was recently moved out of the WHO ISM category and into its own category under SM.9 In SSM, two or more B findings, but no C findings (Table 2) are found and there is a greater possibility that the disease will progress to a more aggressive variant.

**Advanced Systemic Mastocytosis Variants**

**SM WITH AN ASSOCIATED HEMATOLOGIC NEOPLASM (SM-AHN)**

SM-AHN is the recently updated term for SM-AHNMD from the 2016 WHO classification of mastocytosis.9 These patients fit the criteria for SM and they fit the WHO criteria for myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), MDS/MPN overlap disorder, or acute myeloid leukemia (AML), with or without skin lesions.8, 18, 20 Patients are treated for both the SM component and for the associated hematologic neoplasm.

**AGGRESSIVE SYSTEMIC MASTOCYTOSIS**

In this rare variant, aggressive systemic mastocytosis (ASM) patients fit the criteria for SM, with or without skin lesions, and also meet criteria for one or more C findings (Table 2).8 Patients with ASM often require chemotherapy.

**MAST CELL LEUKEMIA**

In this extremely 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.8, 21, 22 The mast cells have malignant features. A 2014 international consensus proposal recommends that MCL be separated into acute and chronic23 subvariants based on whether or not C findings (Table 2) are present.21 In addition, it recommends a distinction between a primary form of MCL and a secondary form that evolves from an existing mast cell neoplasm, such as ASM or mast cell sarcoma. There is a prognostic pre-phase identified in patients with ASM with 5-19% mast cells in bone marrow smears, associated with rapid progression. It has been proposed that this condition be called “ASM in transformation to MCL” (ASM-t). Prognosis can be variable based on the form of disease; life expectancy has been extended, in some cases, due to advances in cytoreductive therapy.24 It is important to note that myelomastocytic leukemia (MML), which is a differential diagnosis, is not regarded by mast cell disease specialists as a subvariant of MCL or SM and should be considered a secondary condition.21

**References**


Mast Cell Sarcoma

Mast cell sarcoma is a rare tumor that may present in many different anatomic locations and age groups, and prognosis is generally poor. Mast cell sarcoma is often misdiagnosed because the presenting cells bear little resemblance to normal mast cells and spindle-shaped mast cells frequently seen in systemic mastocytosis. The cells of mast cell sarcoma more closely resemble “atypical type II mast cells” or “promastocytes” that are associated with some cases of aggressive systemic mastocytosis. Pathological examination of the tumor has shown it to be highly malignant with an aggressive growth pattern. 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.

References


Mast Cell Activation Syndrome Variants

**PRIMARY MCAS**

Primary MCAS results from a clonal population of mast cells, where a genetic alteration in the cells exists, and may be due to mastocytosis or to monoclonal Mast Cell Activation Syndrome (MMAS). Primary MCAS with mastocytosis can be diagnosed if the patient fulfills criteria for MCAS and fulfills the WHO criteria for mastocytosis. MMAS is a distinct disease characterized by the presence of abnormal mast cells and fulfillment of criteria for MCAS, but where sufficient criteria for a diagnosis of mastocytosis are not identified.1-10

**SECONDARY MCAS**

Secondary MCAS is diagnosed when mast cell activation occurs as an indirect result of another disease or condition.1-3, 9, 11 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 IgE-dependent allergy as a cause of secondary MCAS, other diseases that can cause secondary MCAS have been reviewed in the literature.1-3, 11

**IDIOPATHIC MCAS**

Idiopathic MCAS is proposed as a final diagnosis after proposed MCAS criteria have been fulfilled and a thorough evaluation has excluded the possibility of another known underlying cause for this activation.2

12 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 disease specialists.1-3, 9-13 Review of other causes of MCAS to aid physicians in evaluation for the exclusionary diagnosis of idiopathic MCAS have also been provided.1, 3, 10

**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.12, 14, 16 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 disease. 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.13, 14 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,2 such that obtaining laboratory evidence of the event can prove difficult in many circumstances. Some specialists 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.12 If a patient responds well to anti-mediator treatment and fulfills the other proposed criteria,2 with the exception of displaying a rise in mediators, then a diagnosis of idiopathic MCAS remains open for consideration, as long as other diagnoses continue to be considered (please see Valent article noted below for more information on differential diagnoses). The patient should be periodically monitored to try to capture a rise in any of the mediators for which commercial testing is both available and recognized as a widely accepted diagnostic standard.12

Even the co-criterion requiring a response to mast cell targeted therapy can be difficult to obtain in some patients. Sometimes multiple mast cell (or mast cell mediator) blocking therapies must be tried before successful symptom resolution is attained.3, 16 Also, it is reported in another study, 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.10

Please see the following article for more information on mast cell activation syndromes, including potential causes, symptoms, variants, effects of comorbidities and other possible diagnoses to exclude:

References


Hereditary Alpha Tryptasemia (HaT)

Tryptase is a protein made primarily by mast cells and can be used as a marker for mast cell activation. Hereditary alpha tryptasemia is an inherited genetic mutation causing extra copies of the alpha tryptase gene (TPSAB1), leading to increased levels of tryptase in the blood. There is a great variability from person to person with duplications or triplications in terms of symptoms. If a patient’s blood tryptase level is above 10 ng/ml and he or she has another relative who has an elevated level, the patient is more likely to have hereditary alpha tryptasemia. Some patients with hereditary alpha tryptasemia may manifest the following symptoms: allergic-like symptoms such as skin itching, flushing, hives, and even anaphylaxis; gastrointestinal (GI) symptoms such as bloating, abdominal pain, diarrhea and/or constipation (frequently diagnosed as irritable bowel syndrome or IBS), heartburn, reflux, and difficulty swallowing; connective tissue symptoms such as hypermobile joints and scoliosis; cardiac symptoms such as a racing or pounding heartbeat or blood pressure swings, sometimes with fainting; as well as anxiety, depression, chronic pain or panic attacks. It is not clear the extent to which activated mast cells contribute to this disease, nor whether mast cell activation plays any role in symptoms, but this is an area of ongoing research. Many patients do respond to mast cell mediator targeted medications. If your serum tryptase is 8 ng/ml or greater, there is a commercial test offered by Gene by Gene labs. Symptoms are treated individually and definitive treatments have yet to be identified for hereditary alpha tryptasemia. [https://www.niaid.nih.gov/research/hereditary-alpha-tryptasemia-faq]
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. This activation can occur in a healthy person, for example in response to a mosquito bite, and in patients with both mastocytosis and mast cell activation syndrome (MCAS). Patients with mastocytosis have extra mast cells that can activate and release their mediators, in addition to the possibility of mast cells that may more readily release mediators, resulting in increased mediator-induced symptoms. Patients with MCAS may also have mast cells that are signaled to release their mediators more easily; this may depend on genetics, tissue location of the reacting mast cells, the trigger that initiates the response, or even coexisting conditions. Symptomatology can arise from both mediator release and/or from mast cell proliferation, accumulation and infiltration in tissues, depending on the form of mast cell disease. Individuals with HaT may have higher blood tryptase levels associated with more alpha tryptase copies and they may report symptoms in multiple organ systems similar to those affected by SM and MCAS but also including symptoms of dysautonomia and connective tissue disease. Triggers can be common to patients with mastocytosis, MCAS, and HaT, but may be different for each patient.

**Figure 1. Some Potential Mast Cell Triggers**

- Exercise
- Fatigue
- Food or beverages, including alcohol
- Mechanical irritation, friction, vibration
- Infections (viral, bacterial or fungal)
- Heat, cold or sudden temperature changes, Sun/sunlight
- Stress: emotional, physical, including pain, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)
- Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes
- Natural odors, chemical odors, perfumes and scents
- Venoms (bee, wasp, mixed vespid, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitoes and fleas, etc.)
Mast Cell Mediator Symptoms

The myriad symptoms patients with mast cell diseases experience during mast cell activation can wreak havoc on patients on a daily basis, and multiple organ systems, including pulmonary, cardiovascular, dermatologic, gastrointestinal, musculoskeletal, and neurologic can be involved. Table 1 lists some potential effects linked to specific mediators.1, 8-15 Symptoms (Table 2) may include, but are not limited to: flushing of the face, neck, and chest; headache; tachycardia and chest pain; abdominal pain, bloating, gastrointestinal reflux disease (GERD), diarrhea, vomiting; uterine cramps or bleeding; rashes, including maculopapular cutaneous mastocytosis (MPCM)/urticaria pigmentosa (UP), telangiectatic lesions; bone/muscle pain, osteosclerosis, osteopenia, osteoporosis; itching, +/- rash; blood pressure instability; brain fog, cognitive dysfunction; anxiety/depression; lightheadedness, syncope; and the most life-threatening symptom, anaphylaxis. Please note that it is not yet clear if the process of mast cell activation plays a role in the presentation of these symptoms in HaT. These symptoms may appear as acute (as in anaphylaxis, see Table 3) 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.

Table 1. Possible Effects of Some Mast Cell Mediators15, 16

<table>
<thead>
<tr>
<th>MEDIATOR</th>
<th>POSSIBLE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Flushing, itching, diarrhea, hypotension</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Flushing, bone pain, brain fog, cramping</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Osteoporosis, skin lesions</td>
</tr>
<tr>
<td>Interleukins</td>
<td>Fatigue, weight loss, enlarged lymph nodes</td>
</tr>
<tr>
<td>Heparin</td>
<td>Osteoporosis, problems with clotting/bleeding</td>
</tr>
<tr>
<td>Tumor Necrosis Factor-α</td>
<td>Fatigue, headaches, body aches</td>
</tr>
</tbody>
</table>

This mediator list is by no means complete and serves as an example. Mast cells secrete many mediators responsible for numerous symptoms within different organ systems.

Table 2. Mast Cell Mediator Symptoms14, 15

<table>
<thead>
<tr>
<th>MAST CELL MEDIATOR SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANAPHYLAXIS</td>
</tr>
<tr>
<td>Flushing of the face, neck, and chest</td>
</tr>
<tr>
<td>Itching, +/- rash</td>
</tr>
<tr>
<td>Hives, skin rashes</td>
</tr>
<tr>
<td>Angioedema (swelling)</td>
</tr>
<tr>
<td>Nasal itching and congestion</td>
</tr>
<tr>
<td>Wheezing and shortness of breath</td>
</tr>
<tr>
<td>Throat itching and swelling</td>
</tr>
<tr>
<td>Headache and/or brain fog, cognitive dysfunction, anxiety, depression</td>
</tr>
<tr>
<td>Diarrhea, nausea, vomiting, abdominal pain, bloating, gastrointestinal reflux disease (GERD)</td>
</tr>
<tr>
<td>Bone/muscle pain, osteosclerosis, osteopenia, osteoporosis</td>
</tr>
<tr>
<td>Light-headedness, syncope/fainting</td>
</tr>
<tr>
<td>Tachycardia (rapid heart rate), chest pain</td>
</tr>
<tr>
<td>Low blood pressure, high blood pressure at the start of a reaction, blood pressure instability</td>
</tr>
<tr>
<td>Uterine cramps or bleeding</td>
</tr>
</tbody>
</table>

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

Table 3. When Does this Become Anaphylaxis?

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

<table>
<thead>
<tr>
<th>MOUTH</th>
<th>Itching, swelling of lips and/or tongue</th>
</tr>
</thead>
<tbody>
<tr>
<td>THROAT*</td>
<td>Itching, tightness/closure, hoarseness</td>
</tr>
<tr>
<td>SKIN</td>
<td>Itching, hives, redness, swelling</td>
</tr>
<tr>
<td>GUT</td>
<td>Vomiting, diarrhea, cramps</td>
</tr>
<tr>
<td>LUNG*</td>
<td>Shortness of breath, cough, wheeze</td>
</tr>
<tr>
<td>HEART*</td>
<td>Weak pulse, dizziness, passing out</td>
</tr>
</tbody>
</table>

Only a few symptoms may be present. Severity of symptoms can change quickly. *Some symptoms can be life-threatening. ACT FAST! Use your anaphylaxis action plan!*7

Information from Table 3 taken from the American Academy of Allergy, Asthma and Immunology (AAAAI) Anaphylaxis Emergency Action Plan17 and the Anaphylaxis Guidelines Pocketcard.18

An AAAAI Anaphylaxis Card (http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/Anaphylaxis-Card.pdf) in English and Spanish is also available.

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SIGNS AND SYMPTOMS OF MAST CELL PROLIFERATION, ACCUMULATION AND INFILTRATION (MASTOCYTOSIS)

Advanced disease symptoms may include the following signs of mast cell proliferation, accumulation and infiltration: anemia, thrombocytopenia, ascites, bone fractures, gastrointestinal abnormalities, and enlargement of the liver, spleen, and lymph nodes. Mast cell proliferation, accumulation and infiltration can occur in systemic mastocytosis (SM), smoldering SM (SSM), aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN) [previously called “SM with associated clonal hematologic non mast cell lineage disease” (SM-AHNMD)], or mast cell leukemia (MCL). B and C findings (see Systemic Mastocytosis Variants section), in addition to meeting the criteria for SM (see Overview section), clearly define these signs and assist physicians with the diagnosis.

References


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Tests

First and foremost, a careful examination of the skin should be undertaken, looking for characteristic lesions of mastocytosis. If lesions are found, the physician should stroke the lesion firmly with a tongue depressor 5 or 6 times to see if it urticates (Darier’s sign). However, flushing and systemic low blood pressure can result from attempts to identify Darier’s sign in young children who have cutaneous mastocytoma or a polymorphic variant of maculopapular cutaneous mastocytosis with nodular lesions, such that this test should be avoided in these patients.1, 2 Darier’s sign is positive in almost all children and most of the adults who have skin involvement in mastocytosis. An international consensus task force of mast cell disease specialists has recently proposed that Darier’s sign be included as part of the major criterion for diagnosing skin involvement in mastocytosis patients.2 Clear areas of skin can be stroked in the same way noted above to check for dermatographism, or skin writing, in which the area stroked becomes inflamed. Darier’s sign and dermatographism are characteristic cutaneous symptoms in mast cell diseases.

Tests for Mast Cell Activation and/or Mast Cell Activation Syndrome (MCAS) Diagnostic Workup

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.3-5 An international consensus article provides a method for calculating the required minimum rise in serum tryptase:5

After a reaction, a level of serum tryptase that is a minimum of 20% above the basal serum tryptase level, plus 2 ng/ml, will meet the second criterion for a mast cell activation event. For example, if a patient had a basal (baseline level, at least 24 hours after a reaction) serum tryptase level of 8 ng/ml, a 20% rise, plus 2 ng/ml, would be 11.6 ng/ml. To meet the above criterion for serum tryptase, the patient would need a post-reaction serum tryptase level above 11.6 ng/ml. The calculation would be conducted as follows:

\[
\text{After a reaction, level of serum tryptase that is a minimum of 20\% above the basal serum tryptase level, plus 2 ng/ml, will meet the second criterion for a mast cell activation event. For example, if a patient had a basal (baseline level, at least 24 hours after a reaction) serum tryptase level of 8 ng/ml, a 20\% rise, plus 2 ng/ml, would be 11.6 ng/ml. To meet the above criterion for serum tryptase, the patient would need a post-reaction serum tryptase level above 11.6 ng/ml. The calculation would be conducted as follows:}
\]

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-D2, or its metabolite, 11β-prostaglandin-F2α (24-hour or spot 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.5, 6 Some practitioners currently utilize other tests to make a diagnosis of mast cell activation. While we strongly recognize that we are limited in that there are many mast cell mediators, and yet we have commercial tests available for less than five of them here in the US, The Mastocytosis Society, Inc. (TMS) cannot endorse the use of other mediator markers as diagnostic tools until they have been adequately evaluated and proven as valid for mast cell diseases in sound, scientific research. TMS strongly supports and currently funds research to identify better markers for mast cell activation.

TMS does recognize, however, that capturing a mediator rise is not always easy, and depends on many factors, internal and environmental. We have seen 24-hour urine samples test negative simply because the lab technician did not refrigerate the sample in a timely manner (when the test was repeated and handled properly, the result was positive). Therefore, we support the use of a clinical diagnosis and advise that the patient continues to be treated when the following criteria have been met.7

Continued on page 22
• An exhaustive work-up has ruled out other medical conditions with similar symptoms and presentations
• The patient has exhibited consistent symptoms of mast cell activation in 2 or more organ systems during the same period of time, such as skin, gastrointestinal tract, central nervous system, etc.
• The patient responds to antimeriator therapy
• The patient is monitored on a regular basis, with testing for mediator rises performed periodically, by a mast cell or other specialist and/or in conjunction with an established local allergist or other physician
• The patient is evaluated for other disease processes on an ongoing basis in order to be inclusive of any new changes in the patient’s condition

Tests for Clonal Mast Cell Diseases Such as Systemic Mastocytosis or Monoclonal MCAS

Bone Marrow Biopsy

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

KIT Mutation Testing

To understand why KIT testing is necessary, one must first understand the difference between clonal and non-clonal mast cell diseases. Clonal means that there is a defect in a person’s mast cell DNA, which results in their mast cells having abnormal characteristics. Although the most common defect seen in mast cell disease is KIT D816V, it is not the only one that can result in an abnormal disease process. Numerous other mutations in KIT have been associated with mastocytosis, and in the absence of a KIT D816V mutation, other testing can be performed to identify them, including KIT sequencing. If there is no change (no mutation, such as a KIT mutation) identified in the mast cell DNA, but the patient experiences mast cell activation, this may be non-clonal disease, such as idiopathic mast cell activation syndrome.

There has been a peptide nucleic acid mediated PCR based test available for years that can identify the KIT D816V mutation in peripheral blood, and it has been able to detect the mutation in 44% of systemic mastocytosis patients tested. A newer test, an allele-specific oligonucleotide qPCR test, has proven to be much more sensitive and reliable. Patients with indolent systemic mastocytosis with skin involvement, for example, were

In patients who demonstrate a mediator rise, mediator testing should be repeated periodically.
found to have the KIT D816V mutation 92% of the time using the newer allele-specific qPCR blood test.\textsuperscript{14}

Although the more sensitive test for the KIT D816V mutation (the allele-specific qPCR, with a sensitivity of 0.01%) that can be performed in peripheral blood samples has been developed, is not yet widely available here in the US. However, Mayo Clinic in Rochester, MN can perform the allele-specific oligonucleotide PCR (ASO-PCR) test for KIT D816V and the test may be available through several other labs in the US. Currently in the US, the result is often reported as either positive or negative, although in a research setting, results can be presented in more detail as an “allelic frequency”, which is essentially a measure of the extent to which the mutation is present versus KIT without that mutation (the allelic frequency can help in determining disease prognosis). It is important to note that receiving a negative test does not rule out a mast cell disease.\textsuperscript{13, 15} If an adult with systemic mastocytosis does not test positive for the KIT D816V mutation using sensitive testing methods, then sequencing of KIT might be considered.

Knowing the KIT mutation status can be very important when considering therapeutic options such as new medications and chemotherapy. The development of the allele-specific qPCR test will make peripheral blood KIT testing more widely available in the near future. More information on the use of KIT mutation testing in mast cell diseases (including potential use in prognosis) is available in published recommendations from the European Competence Network on Mastocytosis.

Routine and Follow-up Testing for Systemic Mastocytosis (SM) and Smoldering SM

Examinations should occur periodically and include:\textsuperscript{13}

- Dermatological exam (with stroking for Darier’s sign)
- Careful palpation of the liver, spleen and lymph nodes
- A full neuropsychological evaluation
- CBC with differential

- Serum tryptase and 24-hour or spot urines for N-methyl histamine, prostaglandin D2 (PGD2), 11β-prostaglandin F\textsubscript{2α}
- Liver function tests, serum albumin, serum LDH, and serum alkaline phosphatase
- Blood chemistries
- Total immunoglobulins or total IgE, if indicated by previous testing
- DEXA scans for bone density; nuclear medicine bone scan, if indicated
- Bone marrow biopsy with flow cytometry and cytology, when indicated
- Allele-specific qPCR for KIT D816V mutation in peripheral blood/bone marrow, if not already performed; KIT sequencing, if indicated\textsuperscript{13}
- CT scan/ultrasound, if indicated
- Other tests may be performed, as indicated, if there is a suspected hematologic disorder or to evaluate the individual patient’s symptoms.

Diagnostic Workup for Advanced Systemic Mastocytosis Variants or Associated Hematological Disorders\textsuperscript{1, 13, 16, 17}

When advanced disease or an associated hematological disorder is suspected, further evaluation of the patient beyond a bone marrow biopsy and aspirate with flow cytometry may include:

- Comprehensive bloodwork
- X-ray or CT scan of the chest, looking for evidence of significantly enlarged lymph nodes (greater than 2 cm in diameter)
- X-ray, nuclear medicine bone scan of the skeletal system, or bone density scan looking for osteoporosis, osteosclerosis, or areas where calcium has been completely lost from bone
- CT scan or ultrasound of the abdomen, looking for enlarged liver or spleen, enlarged lymph nodes, or the collection of fluid

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Tests

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• 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.18

• Other tests may include next-generation sequencing and myeloid gene panels for additional genetic lesions.

References


Mast Cell Activation/Mediator Release Symptoms

Controlling symptoms of mast cell activation/mediator release starts with avoiding the triggers which will initiate mast cell activation, and the triggers can be very individual. Avoiding heat, cold, abrupt changes in temperature, sunlight, strong odors/perfumes and chemical smells can help many patients. Caution must be taken around venomous creatures such as bees, wasps, hornets, spiders, jellyfish and snakes, etc. Stress and fatigue can be major triggers for many patients, as can viruses, bacterial and fungal infections. Sometimes a simple change in routine can be a trigger.

Many foods can trigger mast cells to activate and release their mediators; shellfish, peanuts, tree nuts, citrus, and high histamine foods are high on the list of potential triggers known to bother some people, but not others. Medications to be taken with caution include NSAIDs such as ibuprofen, toradol, aspirin (this can be confusing, because aspirin can also be used as a treatment for those with high prostaglandin levels; when used as a treatment it must be started under the supervision of a physician!), opioid narcotics, alcohol, the intravenous form of vancomycin (the oral form is usually fine), some anesthetics, some antibiotics, and topical agents, like benzocaine. However, everyone is different. Anyone can react to anything, and a patient can even react to something that he or she has never reacted to before. Encourage your patients to always have someone with them when taking a new medication, starting a new treatment, or traveling to a new place.

Patients are often frustrated by their inability to determine what trigger activated their mast cells. In that situation, treat the symptoms, advise rest, tell the patient to be watchful for any recurrence of symptoms (bi-phasic reaction) and advise the patient to keep a diary of foods, medications, symptoms and possible triggers.

In addition to avoiding triggers, further treatment of mastocytosis depends on the symptoms and the classification of disease. Symptoms of mast cell activation/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 self-injectable epinephrine, unless otherwise contraindicated (glucagon may need to be administered for patients on beta-blockers). Patients should also be instructed on how to self-administer the epinephrine while lying down, to maximize rapid absorption of the drug.

Every patient should carry a physician-signed American Academy of Allergy, Asthma and Immunology Anaphylaxis Action Plan at all times. http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/Anaphylaxis-Emergency-Action-Plan.pdf

Treatment of mast cell mediator-related symptoms are the same for mastocytosis, MCAS and HaT.

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There has been growing recognition of the detrimental effects on cognition (mental clouding and other cognitive impairments) caused by long term use of antihistamines. A high risk group of patients 65 years and older (defined as patients taking 50 mg per day for 3 years diphenhydramine or doxepin or 25 mg for 6 years), were found to have a significant association between diphenhydramine use and cognitive impairment. Similarly, high doses of sedating antihistamines such as diphenhydramine can cause increased seizure activity, seen mostly in children. In addition, a tolerance to or a dependence upon diphenhydramine may result in a need for even higher doses. Caution and restraint must be used when taking antihistamines long term in order to help preserve neurological function. While these drugs are crucial for their antimediator effects, they should be titrated to the lowest dose necessary to achieve control of mast cell activation symptoms.

**Additional Symptoms of Indolent Systemic Mastocytosis**

A suggested order of treatment options for adult patients with indolent systemic mastocytosis, aimed at symptom control, and including suggested therapies for osteoporosis, can be found in table 3 of this article: http://onlinelibrary.wiley.com/doi/10.1002/ajh.23931/full from the American Journal of Hematology.

**Advanced Disease**

Therapies exist for smoldering systemic mastocytosis (SSM) and advanced systemic mastocytosis, and promising new treatments are being developed. Prominent among these newer treatments are tyrosine kinase inhibitors (TKIs) targeting the *KIT* kinase (e.g., midostaurin). Imatinib is approved therapy for adult aggressive systemic mastocytosis (ASM) patients lacking the *KIT* D816V mutation or if mutation status is unknown. Additional standard therapies for advanced variants are interferon, the chemotherapeutic agent cladribine, and tyrosine kinase inhibitors such as midostaurin. These chemotherapeutic agents are used in combination with antimediator therapy to control symptoms and reduce the overall mast cell burden. In patients with systemic mastocytosis with associated clonal hematologic non-mast cell lineage disease (SM-AHNMD)/systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), therapy selection usually depends on the associated disease, which is commonly more aggressive than the SM part. Mast cell leukemia and sarcoma require a polychemotherapy approach.

**References**

Medications To Treat Mast Cell Diseases

**ALL PATIENTS:**

Self-Injectable Epinephrine (two doses; e.g., EpiPen®/EpiPen Jr®) should be carried by all patients with a mast cell disease at all times, even if previous anaphylaxis has not occurred. Both the patient and family members/caregivers should be trained on administering the epinephrine!

Please visit the American Academy of Allergy, Asthma and Immunology (AAAAI) website for more information on anaphylaxis.

http://www.aaaai.org/conditions-and-treatments/allergies/anaphylaxis

Basic Medications for Symptomatic Patients with Mast Cell Diseases

- **H1 antihistamines:** help with itching, abdominal pain, flushing, headaches, brain fog
- **H2 antihistamines:** help with gastrointestinal symptoms and overall mast cell stability (all mast cell activation symptoms)
- **Mast cell stabilizers:** help with stomach and intestinal symptoms and brain fog
- **Leukotriene inhibitors:** help with respiratory symptoms and overall mast cell stability (all mast cell activation symptoms)
- **Aspirin therapy (under direct supervision of a physician):** if tolerated and if prostaglandins are elevated, helps with flushing, brain fog and bone pain

Note: The H1 and H2 antihistamines are necessary to stabilize receptors on the mast cell. Therefore, if additional medication is required for control of gastroesophageal reflux (GERD), a proton pump inhibitor may be added to this protocol, but it cannot replace the H2 antihistamine.

Please see Table 1- Table 6 for lists of some specific drugs in these different categories.

Please see Table 7 for a list of some specific drugs for advanced systemic mastocytosis.

### Table 1. Some First Generation H1 Antihistamines

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atarax®</td>
<td>Hydroxyzine hydrochloride</td>
</tr>
<tr>
<td>Benadryl®</td>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>Chlor-trimeton®</td>
<td>Chlornephrinamide</td>
</tr>
<tr>
<td>Doxepin®, Sinequan®</td>
<td>Doxepin hydrochloride</td>
</tr>
<tr>
<td>Tavist®</td>
<td>Clemastine</td>
</tr>
</tbody>
</table>

### Table 2. Some Second Generation H1 Antihistamines (may tend to cause less drowsiness)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegra®</td>
<td>Fexofenadine</td>
</tr>
<tr>
<td>Claritin®</td>
<td>Loratidin</td>
</tr>
<tr>
<td>Clarinex®</td>
<td>Desloratidin</td>
</tr>
<tr>
<td>Zaditor®/Zaditen® (in Europe)*</td>
<td>Ketotifen</td>
</tr>
<tr>
<td>Xyzal®</td>
<td>Levocetirizine</td>
</tr>
<tr>
<td>Zyrtec®</td>
<td>Cetirizine</td>
</tr>
</tbody>
</table>

*Zaditor® is only available in the US as eye drops; Zaditen® is available by prescription, but it must be obtained from a compounding pharmacy or from abroad.

### Table 3. Some H2 Antihistamines

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axid®</td>
<td>Nizatidine</td>
</tr>
<tr>
<td>Pepcid®</td>
<td>Famotidine</td>
</tr>
<tr>
<td>Tagamet®</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Zantac®</td>
<td>Ranitidine</td>
</tr>
</tbody>
</table>

Continued on page 28
### Table 4. Mast Cell Stabilizers

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocrom®</td>
<td>Oral cromolyn sodium</td>
</tr>
<tr>
<td>Zaditor®/Zaditen® (in Europe)*</td>
<td>Ketotifen</td>
</tr>
<tr>
<td>Algonot, Neuroprotect, etc.</td>
<td>Food supplements containing bioflavonoids such as quercetin and luteolin</td>
</tr>
<tr>
<td>Aspirin; ASA</td>
<td>Aspirin, acetysalicylic acid (for those with high prostaglandin levels; aspirin therapy must be initiated under the direct supervision of a physician!)</td>
</tr>
</tbody>
</table>

* Zaditor® is only available in the US as eye drops; Zaditen® is available by prescription, but it must be obtained from a compounding pharmacy or from abroad.

### Table 5. Some Leukotriene Inhibitors

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singulair®</td>
<td>Montelukast</td>
</tr>
<tr>
<td>Accolate®</td>
<td>Zafirlukast</td>
</tr>
<tr>
<td>Zyflo®/Zyflo CR®</td>
<td>Zileuton</td>
</tr>
</tbody>
</table>

### Table 6. Proton Pump Inhibitors to Help with GERD (Gastroesophageal Reflux)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciphex®</td>
<td>Rabeprazole</td>
</tr>
<tr>
<td>Dexilant®</td>
<td>Dxlansoprazole</td>
</tr>
<tr>
<td>Nexium®</td>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Prevacid®</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Prilosec®</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Protonix®</td>
<td>Pantoprazole</td>
</tr>
</tbody>
</table>

### Table 7. Some Chemotherapy Drugs for Selected Patients with Smoldering and Advanced Variants of Systemic Mastocytosis1,5

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleevec®</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Masivet®</td>
<td>Masitinib</td>
</tr>
<tr>
<td>Sprycel®</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>Tasigna®</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>Rydapt®</td>
<td>Midostaurin</td>
</tr>
<tr>
<td>Hydrea®</td>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>Leustatin®, Leustat®, Litak®</td>
<td>Cladribine, 2-CDA</td>
</tr>
<tr>
<td>Intron®</td>
<td>Interferon Alfa-2b</td>
</tr>
</tbody>
</table>

There are several more therapies in the pipeline, including additional tyrosine kinase inhibitors and other targeted therapies.

Sometimes symptoms change, and it becomes necessary to increase or decrease doses of medications, or to add additional medications to a patient’s prescribed protocol. Sometimes a simple adjustment made by a mast cell specialist can make a significant difference in a patient’s symptoms. Please reinforce with your patients that while it is tempting to change dosing regimens on their own, it is important that they work closely with their physician to achieve the safest most effective outcome.

### References

Pediatric mast cell diseases, 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). A fairly common genetic trait, hereditary alpha-tryptasemia (HaT), is caused by an increase in the copy number of the gene encoding alpha-tryptase. HaT causes elevated basal serum tryptase and has been associated with mast cell disease. Mast cells are instrumental in mediating anaphylaxis, and children with mast cell diseases may be at higher risk to develop both provoked and unprovoked episodes of anaphylaxis. A child with mastocytosis whose disease appears to be confined to the skin may still exhibit systemic symptoms due to mast cell mediator release. Symptoms common to pediatric mast cell diseases may include flushing of the face and neck, dermatographism, gastrointestinal complaints (such as diarrhea, abdominal pain, nausea, gastroesophageal reflux (GERD) and bloating), pruritis, dyspnea, headache, lethargy, fatigue, and neuropsychiatric symptoms. In addition, patients affected by HaT may also demonstrate symptoms of a connective tissue disorder and dysautonomia/postural orthostatic tachycardia syndrome (POTS). Many children with mast cell diseases may complain of generally feeling unwell, may have difficulty identifying or localizing specific symptoms, or may seem to present with several symptoms of mast cell activation, while others may seem to have very few or none.

Pediatric cutaneous mastocytosis (CM) encompasses a variety of clinical manifestations. In children, some of these varieties will spontaneously resolve before young adulthood, some will persist into adulthood as cutaneous disease only, some will be diagnosed in childhood or later as systemic mastocytosis (SM), mostly indolent, and some will evolve into well-differentiated systemic mastocytosis (WDSM).

**DEFINITIONS**

**Darier’s sign** is an important diagnostic finding of patients with mastocytosis. It can be elicited by stroking an existing CM lesion with a wooden tongue depressor, approximately 5 times with moderate pressure. Within a few minutes, a wheal and flare reaction of the lesion will be seen. A positive Darier’s sign is usually seen in pediatric patients, but not always in adults. It may be decreased by treatment with antihistamines. If the testing procedure for Darier’s sign is not done properly, false positives or false negatives may result. Darier’s sign is to be applied to the evaluation of fixed cutaneous lesions except in the case of a pediatric patient with cutaneous mastocytoma or nodular lesions. Testing for Darier’s sign may provoke a systemic reaction and should either be performed with the greatest of caution or avoided.

**Dermatographism** is a skin reaction characterized by a wheal and flare response when normal skin, not affected by skin lesions, is stroked with a tongue depressor, finger nails or other instrument. The nick-name for dermatographism is skin writing disease.

A *macule* is a lesion that is flat and even with the surrounding skin, identified by a change in color compared to the surrounding skin.

Continued on page 30
A **papule** is a small bump or elevated lesion, up to 1 cm in diameter, containing no visible fluid.

A **nodule** is a growth of abnormal tissue just below the skin.

A **bulla** is a large blister filled with fluid.

**Telangiectasia** is a vascular lesion formed by dilatation of a group of small blood vessels.

**AGE OF ONSET**

- Pediatric CM is commonly diagnosed prior to age two.
  - Pediatric disease is seen at a ratio of 1.4 males:1 female.\(^6\)
  - No race has been found to be predominant.\(^7\)
- Pediatric mast cell activation syndrome (MCAS) can be diagnosed at any age.

**PEDIATRIC CUTANEOUS MASTOCYTOSIS VARIANTS**

**Presentation:**
In 90% of the cases, the typical presentation involves cutaneous manifestations (skin lesions). These may include:

**Cutaneous Mastocytoma**\(^1\)
- Usually present at birth
- Elevated lesion(s) *(up to a total of three lesions)* which usually resolves during childhood
- Four cutaneous mastocytomas or more become a diagnosis of MPCM (see below)
- Multiple mastocytomas may evolve into adult WDSM\(^4\)

**Maculopapular Cutaneous Mastocytosis (MPCM)/Urticaria Pigmentosa (UP)\(^1\)**
- 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\(^7\)
- Encompasses several clinical entities with different outcomes, including: pitted melanotic macules, reddish brown telangiectatic macules, lightly pigmented papules, brownish papules, and small nodules
- This group is divided into two sub-variants
  - Monomorphic variant (Monomorphic means one basic shape/size)
    - Mostly seen in adults and in a small subgroup of children
    - Small maculopapular lesions, similar in shape, size and color
    - Children presenting with this form may have increased serum tryptase and a tendency toward systemic disease that persists into adulthood
    - The type of lesions can vary during the course of the disease, i.e., nodules during infancy may turn into plaques at age 6
  - Polymorphic variant (Polymorphic means different shapes/sizes)
    - Mostly seen in children
    - Can be macular, plaque or nodular, with lesions of variable shape, color and size
    - Although, children typically express mutations in exon 8, 9, 11 or 17 of the KIT gene, KIT mutations may be negative
    - Usually involving head, neck and extremities
    - May involve blistering upon irritation until 3 years of age
    - Prognosis is favorable with regression of disease in adolescence or young adulthood
Diffuse Cutaneous Mastocytosis (DCM)

- Skin thickened, hyperpigmented and diffusely infiltrated
- Can involve up to 100% of the skin with the trunk, head and scalp heavily affected
- Can appear at birth or early infancy; may persist into adulthood, possibly as WDSM
- Blisters, some of which are hemorrhagic; bullae may be present and dermatographism may be prominent
- Flushing is a common symptom
- Tryptase may be elevated due to increased mast cell burden in the skin, as most patients do not have systemic organ involvement; however, this elevation may also be indicative of WDSM

PEDIATRIC SYSTEMIC MASTOCYTOSIS

Approximately 15% of children with who are diagnosed with mastocytosis have disease that is actually systemic mastocytosis (SM), which will then persist into adulthood. As recently as 13 years ago, it was not recognized that pediatric patients could even have systemic disease. We are learning more each day about patients with pediatric SM and will add more to this section as more articles are published.

SYMPTOMS OF MAST CELL ACTIVATION Which May be Seen in Both Pediatric CM and MCAS

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

GUIDELINES FOR DIAGNOSIS

Pediatric Mastocytosis

- 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 (CD117)
- 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, indicated by:
  - abnormal peripheral blood counts, organomegaly, significant lymphadenopathy, severe recurrent systemic mast cell mediator-related symptoms, persistent high tryptase, persistence of disease into adulthood

Pediatric mast cell activation syndrome (MCAS) can be diagnosed at any age.
Pediatric MCAS

- Although specific guidelines do not exist for diagnosing pediatric MCAS, proposed consensus criteria for diagnosing MCAS have been utilized by specialists.\(^2, 10, 11\)
- Three criteria must be met:
  - The patient exhibits symptoms of mast cell activation involving two or more organ systems at the same time, which recur or are always present, cannot be attributed to any other disease or condition and require treatment.\(^2\)
  - The patient demonstrates a rise in either total serum tryptase (above baseline and within one to two hours of a symptomatic episode; see below for calculation method to determine if the rise indicates mast cell activation has occurred) or one or more of the three urinary mediators, n-methyl histamine, prostaglandin-D\(_2\), or its metabolite, 11\(\beta\)-prostaglandin-F\(_2\)\(_\alpha\). Additionally, another mediator test, leukotriene E\(_4\) (LTE\(_4\)), collected as a spot or 24 hour urine after an acute, symptomatic episode is available through the Mayo Clinic.\(^2, 10\)
  - The patient demonstrates a rise in either total serum tryptase (above baseline and within one to two hours of a symptomatic episode; see below for calculation method to determine if the rise indicates mast cell activation has occurred) or one or more of the three urinary mediators, n-methyl histamine, prostaglandin-D\(_2\), or its metabolite, 11\(\beta\)-prostaglandin-F\(_2\)\(_\alpha\). Additionally, another mediator test, leukotriene E\(_4\) (LTE\(_4\)), collected as a spot or 24 hour urine after an acute, symptomatic episode is available through the Mayo Clinic.\(^2, 10\)

Further study is needed to determine if all patients being evaluated for MCAS will demonstrate a rise in one of the five known mast cell mediators (see above) for which validated tests are currently available.\(^8\)

- The consensus article provides a method for calculating the required minimum rise in serum tryptase.\(^2\) After a reaction, a level of serum tryptase that is a minimum of 20% above the basal serum tryptase level, plus 2 ng/ml, will meet the second criterion listed above for a mast cell activation event. For example, if a patient had a basal (baseline level, at least 24 hours after a reaction) serum tryptase level of 8 ng/ml, a 20% rise, plus 2 ng/ml, would be 11.6 ng/ml.

To meet the above criterion for serum tryptase, the patient would need a post-reaction serum tryptase level above 11.6 ng/ml. The calculation would be conducted as follows:

\[
(8 \text{ ng/ml} \times 1.2) + 2 \text{ ng/ml} = 9.6 \text{ ng/ml} + 2 \text{ ng/ml} = 11.6 \text{ ng/ml}
\]

(basal level plus 20%) + additional 2 ng/ml = the serum tryptase level, after a reaction, that must be exceeded in order to meet a rise in serum tryptase considered a mast cell activation event

- The patient must display a response (based on response criteria)\(^3\) to ant mediato r therapy.\(^2, 10\)

Pediatric Hereditary Alpha-Tryptasemia (HaT)

- Patients who suspect they may have HaT should have a baseline (not after a major reaction) serum tryptase blood test drawn. This will have to be ordered by their physician. A serum level greater than 10 ng/ml may be suggestive of HaT, especially in children who have not been diagnosed with mastocytosis. Additionally, a clinical assay to identify an increase in the number of copies of the alpha-tryptase gene is available through the Mayo Clinic.\(^2, 10\)

Further study is needed to determine if all patients being evaluated for MCAS will demonstrate a rise in one of the five known mast cell mediators (see above) for which validated tests are currently available.\(^8\)

- The consensus article provides a method for calculating the required minimum rise in serum tryptase.\(^2\) After a reaction, a level of serum tryptase that is a minimum of 20% above the basal serum tryptase level, plus 2 ng/ml, will meet the second criterion listed above for a mast cell activation event. For example, if a patient had a basal (baseline level, at least 24 hours after a reaction) serum tryptase level of 8 ng/ml, a 20% rise, plus 2 ng/ml, would be 11.6 ng/ml.

SOME POTENTIAL TRIGGERS TO AVOID (VARIES BY PATIENT)

- Heat and/or cold; abrupt changes in temperature; sun/sunlight
- Friction or pressure on the skin; vibration
- Specific foods: very individualized but may include shellfish, high histamine foods such as left-overs, salicylate-containing foods, nuts, peanuts and other potential allergens
• Venoms (bee, wasp, mixed vespid, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitoes and fleas, etc.)
• Bacterial, viral and fungal infections
• Stress: physical, including pain, emotional or environmental
• Fatigue
• Exercise
• Perfumes, odors, natural odors and chemical exposures

TREATMENT GUIDELINES FOR PEDIATRIC MAST CELL DISEASES

• Identification and 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
• UVA/UVB Photolight therapy (treatment option for skin lesions in some pediatric mastocytosis patients only)
• Mast cell stabilizers
  - Oral cromolyn sodium
  - Ketotifen
• Omalizumab
• Injectable epinephrine (to be safe, TMS recommends that 2 doses of injectable epinephrine be prescribed and available at all times (or carried by the child if older) for children with mast cell diseases; this is especially critical for children with SM)
  - EpiPen®/EpiPen Jr® auto injector
• Topical treatments
  - Steroid creams
  - Cromolyn sodium cream 1%-5%
• In children with HaT, treatment for connective tissue disease and autonomic dysfunction, as indicated
• No chemotherapy is indicated in cutaneous or indolent systemic mastocytosis in children, unless clear evidence of progression to aggressive disease is identified

PROGNOSIS

Pediatric Mastocytosis
• Benign course will be seen in approximately 70% of patients.
• In approximately 30% of pediatric mastocytosis cases, disease persists into adulthood, with 15% as disease confined only to the skin, and 15% as disease that starts out as pediatric SM and remains SM.
• Children with extensive bullous lesions appear to be at increased risk of shock or sudden death from anaphylaxis.
• Children with widespread skin lesions (MPCM/UP & DCM) are at increased risk for severe systemic reaction due to potential mast cell mediator release from affected skin.

Pediatric MCAS
• There is no data on prognosis for pediatric patients with MCAS; however all patients with MCAS may be at increased risk for anaphylaxis and a potentially poor outcome. Therefore, these children need to be followed by an allergist familiar with pediatric MCAS, be treated with antimediator therapy when indicated and always carry two doses of injectable epinephrine.
Pediatric Mast Cell Diseases

Continued from page 33

Pediatric HaT
• There has not been sufficient time to study the natural history of HaT. Presently there is no reason to suspect that those with multiple copies of the alpha-tryptase gene will have a shortened lifespan.

SUPPORT SERVICES
• The Mastocytosis Society, Inc. is a 501(c)3, nonprofit organization dedicated to supporting patients affected by Mastocytosis or Mast Cell Activation Diseases, as well as their families, caregivers, and physicians through research, education and advocacy.
• The Mastocytosis Society, Inc. coordinates support groups across the United States. Please visit https://tmsforacure.org/resources/support-groups-2/
• Mastokids.org is a site where parents and caregivers of children with mastocytosis can come to learn, find support, and discover a safe environment to interact with other families.

TMS thanks Mishele Cunningham, RN, BSN, PHN, for her contributions to previous issues of this text.

REFERENCES:


Pediatric Mast Cell Diseases
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Symptoms of Mast Cell Disease Infographic

View more infographics at https://tmsforacure.org/printable-resources-infographics/

Some common symptoms of mast cell disease that are caused by mast cell mediator release:

**NEUROLOGICAL**
- headache
- brain fog
- cognitive dysfunction
- anxiety
- depression

**CUTANEOUS (SKIN)**
- flushing of the face/neck/chest
- hives, skin rash
- itching with or without rash

**EAR/NOSE/THROAT/RESPIRATORY**
- nasal itching and congestion
- throat itching and swelling
- wheezing
- shortness of breath

**GASTROINTESTINAL**
- diarrhea
- nausea
- vomiting
- abdominal pain
- bloating
- gastroesophageal reflux disease (GERD)

**SKELETAL**
- bone/muscle pain
- osteopenia
- osteoporosis

**GYNECOLOGICAL**
- uterine cramps
- bleeding

**CARDIOVASCULAR**
- light-headedness
- syncope (fainting)
- rapid heart rate
- chest pain
- low blood pressure
- high blood pressure at the start of a reaction
- blood pressure instability

**URINARY**
- bladder irritability
- frequent voiding

**SYSTEMIC AND/OR ORGAN SPECIFIC**
- anaphylaxis
- angioedema (swelling)

Symptoms can be sudden and unpredictable in onset.

*LEARN MORE AT tmsforacure.org*
Visual Guide to Diagnosing Mastocytosis

The following pages are a photo journal of examples of how mast cell diseases can present. A majority of the pictures are of skin manifestations of mastocytosis. While cutaneous mastocytosis can include maculopapular cutaneous mastocytosis (MPCM), including urticaria pigmentosa (UP) and telangiectasia macularis eruptiva perstans (TMEP), diffuse cutaneous mastocytosis (DCM), and cutaneous mastocytoma, skin manifestations can also occur in systemic mastocytosis (SM), mast cell activation syndrome (MCAS) and idiopathic anaphylaxis patients.

Most cases of childhood-onset mastocytosis fall into one of the cutaneous mastocytosis categories listed above and may or may not include symptoms of systemic mast cell activation as a result of mediators released from the skin. It should be noted that the formerly used 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 athlete with maculopapular cutaneous lesions, monomorphic type (formerly known as urticaria pigmentosa or UP), during a flare when the lesions are swelling

Pic. 2- Female adult with smoldering systemic mastocytosis (SSM), and typical maculopapular, cutaneous lesions, monomorphic type (formerly called urticaria pigmentosa or UP) during a flare

Pic. 3- Female child with cutaneous mastocytosis and characteristic maculopapular, polymorphic skin lesions (formerly known as urticaria pigmentosa or UP)

Pic. 4- Female child with cutaneous mastocytoma on shoulder, which can present with an elevated lesion which is red or tannish brown
Pic. 5- Male child with cutaneous mastocytosis, characterized by maculopapular cutaneous lesions, polymorphic type (formerly known as urticaria pigmentosa or UP). Note that in some children, during a flare in response to a trigger, lesions may become bullous or blistered.

Pic. 6- Male child with cutaneous mastocytosis with polymorphic lesions and other rashes
Pic. 7- Male child with cutaneous mastocytosis during flare causing blisters in his maculopapular cutaneous lesions

Pic. 8- Male child with mast cell activation syndrome, during flushing episode

Pic. 9- Male child with the maculopapular cutaneous lesions, polymorphic type, consistent with cutaneous mastocytosis (formerly called urticaria pigmentosa or UP)
Pic. 10- Adult female with maculopapular, cutaneous lesions, monomorphic type during a flare

Pic. 11- Female child with maculopapular, polymorphic lesions of cutaneous mastocytosis

Pic. 12- Cutaneous mastocytoma, normal and inflamed

Pic. 13- Female with idiopathic anaphylaxis, hives (urticaria) and dermatographism

For more information on skin manifestations in mastocytosis (including a large selection of photos) and to review the source of our publication’s descriptions of cutaneous mastocytosis variants, please see the following full-text article, which is freely available online:

Medical & Research Specialty Centers for Mast Cell Disease

Please note carefully what each center specializes in. For example, some centers only treat patients with biopsy-confirmed systemic mastocytosis, while others only treat advanced variants. It is indicated below if a center will treat patients for mast cell activation syndrome and whether or not they will treat adults and/or children. Comprehensive centers can do the entire work-up, including evaluation, physical exam, KIT mutation analysis, mediator testing and bone marrow biopsy with flow cytometry, using appropriate stains for tryptase and expression of CD2 and CD25.

**Abbreviations used below:**

MCAS: Mast Cell Activation Syndrome  
CM: Cutaneous Mastocytosis  
SM: Systemic Mastocytosis  
ISM: Indolent Systemic Mastocytosis  
SSM: Smoldering Systemic Mastocytosis  
SM-AHN: Systemic Mastocytosis with an Associated Hematologic Neoplasm  
ASM: Aggressive Systemic Mastocytosis  
MCL: Mast Cell Leukemia  
MCS: Mast Cell Sarcoma  
MPN: Myeloproliferative Neoplasm

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Fax: 720-848-0704

*Specialization:* Adults. ISM, SSM, SM-AHN, ASM and MCL. Diagnosis (bone marrow biopsy can be arranged), treatment, and research.

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*Specialization:* Adults and pediatric. Physician referrals only for CM, biopsy-proven SM, and adult idiopathic anaphylaxis. Diagnosis (bone marrow biopsies), treatment, and research.

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60 Fenwood Rd., Brookline, MA 02115  
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Fax: 617-525-1310

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Contact: Matthew P. Giannetti, MD  
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Brigham and Women's Hospital  
Division of Gastroenterology  
75 Francis St., Boston, MA 02115

Contact: Matthew J. Hamilton, MD  
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Harvard Medical School  
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Fax: 617-264-5277

Dana Farber Cancer Institute  
Hematologic Oncology Program  
450 Brookline Ave., Dana D1B30  
Boston, MA 02215

Contact: Daniel DeAngelo, MD, PhD  
Associate Professor of Medicine  
Harvard Medical School  
Email: daniel_deangelo@dfci.harvard.edu  
Phone: 617-632-6028  
Fax: 617-632-6771

Specialization: Adults. Pediatric (outpatient only at BWH; more complex pediatric cases may be seen in conjunction with Children's Hospital Boston). Physician referral required. All mastocytosis and MCAS; only SM and variants for DFCI. Diagnosis (can arrange bone marrow biopsies), treatment, and research.

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

Contact: Theocharis Theocharides, MD, PhD  
Professor of Pharm. and Internal Medicine  
Email: theocharis.theocharides@tufts.edu  
Phone: 617-636-6866  
Fax: 617-636-2456

Does not see patients in clinic. Available for consultation with physicians.

University of Michigan  
Comprehensive Cancer Center  
Myeloproliferative Neoplasms and Systemic Mastocytosis Clinic  
1500 East Medical Center Drive, Ann Arbor, MI 48109

Contact: Cem Akin, MD, PhD  
Professor of Medicine  
Department of Internal Medicine

Division of Allergy and Clinical Immunology  
24 Frank Lloyd Wright Drive  
PO Box 442, Suite H-2100,  
Ann Arbor, MI 48106-0422  
Email: cemakin@med.umich.edu  
Phone: 734-936-5634  
Phone (new patient coordinator): 734-232-2071  
Fax: 734-647-6263

Specialization: Adults. Biopsy-proven only. ISM, SSM, ASM, SM-AHN, and MCL. Will perform diagnostic bone marrow biopsies for patients with elevated tryptase or biopsy-proven cutaneous disease. Diagnosis, treatment, and research.

Minnesota  
Mayo Clinic Program for Mast Cell and Eosinophil Disorders  
200 First St. SW, Rochester, MN 55905

Mayo Clinic – Allergy Department

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

Contact: Anupama Ravi, MD  
Email: ravi.anupama@mayo.edu

Pediatric Mastocytosis and MCAS

Contact: Thanai Pongdee, MD  
Email: pongdee.thanai@mayo.edu  
Phone: 507-284-9077  
Fax: 507-284-0902

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

Mayo Clinic – Hematology Department

Contact: Animesh Pardanani, MBBS, PhD  
Email: pardanani.animesh@mayo.edu

Specialization: Adults. ISM, SSM, ASM, SM-AHN, and MCL. Will perform diagnostic bone marrow biopsies for patients with elevated tryptase or biopsy-proven cutaneous disease. Diagnosis, treatment, and research.

New York  
Columbia University Medical Center  
New York Presbyterian Hospital  
Herbert Irving Pavilion  
161 Fort Washington Avenue  
Garden Level  
New York, NY 10032

Contact: Mark Heaney, MD, PhD  
Director, Hematology and Medical Oncology Fellowship Program  
Email: mh2192@cumc.columbia.edu  
Phone: 202-305-0566  
Fax: (212) 305-8112

Specialization: Adults with advanced variants: SSM, ASM, SM-AHN, and MCL. Diagnosis, treatment, and research. Specialty area-MPNs.

Ohio  
University of Cincinnati College of Medicine  
231 Albert Sabin Way, ML#563  
Cincinnati, Ohio 45267-0563

Contact: Jonathan Bernstein, MD  
Professor of Clinical Medicine  
Department of Internal Medicine  
Division of Immunology/Allergy  
Email: jonathan.bernstein@uc.edu  
Phone: 513-558-5533  
Fax: 513-558-3799

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

Ohio State University  
Wexner Medical Center  
410 West 10th Avenue,  
Columbus, OH 43210

Contact: Charity Fox, MD  
Associate Professor Internal Medicine  
Pulmonary, Allergy, Critical Care and Sleep Medicine  
charity.fox@osumc.edu  
614-366-3687

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Medical & Research Centers that Treat Patients with Mast Cell Diseases

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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: Adults. Advanced variants of SM only: SSM, SM-AHN, ASM and MCL. Diagnosis, 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
Professor of Internal Medicine
Adjunct Professor of Oncological Sciences
Email: michael.deininger@hsc.utah.edu
Phone: 801-585-3229

Specialization: Adults. Advanced variants of systemic mastocytosis (SM) only: SSM, SM-AHN, ASM and MCL. Diagnosis, treatment, and research.

Virginia
Virginia Commonwealth University
P.O. Box 980263
1250 East Marshall St., Richmond, VA 23298

Contact: Dr. Larry Schwartz, MD, PhD
Professor of Medicine
Chair, Division of Rheumatology, Allergy, and Immunology
Email: lbschwar@vcu.edu
Phone: 804-828-9685
Fax: 804-828-0283

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

INTERNATIONAL (Active Centers)

Europe
European Competence Network on Mastocytosis (ECNM)
www.ecnm.net

North, Central and South America
American Initiative in Mast Cell Diseases (AIM)
www.aimcd.net
Email: info@aimcd.net

Latin America
Aliança Latino-Americana em MAstocitose (ALMA)
President: Ana Mósca de Cequeira, MD
Associate Clinical Professor of Pediatric Dermatology
Hospital Municipal Jesus, Rio de Janeiro, RJ, BRAZIL
Email: almamastocitosis@gmail.com

Hospital das Clinicas, University of São Paulo,
São Paulo, BRAZIL
Contact: Pedro Giavina-Bianchi Jr., MD, PhD
Head of Allergy and Immunology Service
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Email: pbianchi@usp.br

Israel
Technion - Israel Institute of Technology, Haifa
Emek Medical Center, Afula

Contact: Menachem Rottem, MD, PhD
Head of the Allergy, Asthma and Immunology Service
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Email: menachem@rottem.net
Phone: 972-52-8617823

Meir Medical Center, Kfar Saba
Contact: Alon Hershko, MD, PhD
Email: alon.hershko@clalit.org.il

Australia and Asia
Email: info@mastocytosis.org.au

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 diseases. We thank them for their dedication and volunteerism.

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Support Group Contacts

United States

TMSFORACURE.ORG/RESOURCES/SUPPORT-GROUPS-2

Support groups provide a way for individuals suffering from Mast Cell Diseases, and their caregivers and families, to communicate with each other, support each other, provide comfort and often share information that makes their daily lives better. TMS offers a variety of support opportunities which are described on the link listed above.

International

WWW.MASTOCYTOSIS-MCAS.ORG

The International Mastocytosis and Mast Cell Diseases website is an online global platform uniting Mastocytosis and Mast Cell Disease patients, caregivers and health care practitioners from around the world. Here you will find the individual links and contact information for country-specific support groups.

MASTOCYTOSIS, MAST CELL ACTIVATION SYNDROMES, AND HEREDITARY ALPHA TRYPTASEMIA

Medical References

Selected references, listed by topic, that might be of interest to mast cell disease patients, their caregivers, physicians or others may be found at www.tmsforacure.org/research/research-resources.
Mastocytosis is a rare disease in which immune cells known as mast cells abnormally build up in the skin, known as cutaneous mastocytosis (CM), and in the organs results in organ function impairment, as shown by symptoms of pruritus (itching), photosensitivity, and anaphylactic shock.

In almost all patients with SM, a genetic mutation known as KIT D816V is believed to be the root cause of the disease. The genetic mutation is not hereditary, and it is highly unusual for SM to run in families. Today, most patients with SM are treated with symptom relieving medications for GI, skin, and bone marrow symptoms. In more severe cases, mast-cell accumulation in the organs results in organ function impairment.

The signs, symptoms and severity of mastocytosis vary widely, but in more severe cases, mast-cell accumulation can cause internal bleeding, also known as hemoptysis. About 10% of patients with mastocytosis develop symptoms of high blood pressure due to excessive production of histamine, that help activate the immune system and can cause flushing, shortness of breath and anaphylactic shock.

The signs and symptoms of mastocytosis can include:

- Pruritus (itching)
- Photosensitivity
- Rash
- Anaphylactic shock
- flushing
- shortness of breath
- anaphylactic shock

Mastocytosis is a rare disease. It is estimated to affect 1 in 100,000 people in the United States.

Mast Cell Connect is an electronic patient registry created to advance the understanding of mastocytosis, as KIT D816V is believed to be the root cause of the disease. The genetic mutation is not hereditary, and it is highly unusual for SM to run in families. Today, most patients with SM are treated with symptom relieving medications for GI, skin, and bone marrow symptoms. In more severe cases, mast-cell accumulation in the organs results in organ function impairment.

For the disease, there is no cure. However, symptom relieving medications are used to provide symptom relief. For all other questions, contact coordinator@mastcellconnect.org.}

For questions about the goals of the Mast Cell Connect registry, contact the study doctor at mastcellregistry@blueprintmedicines.com or at 617-714-6678.

Questions?

For questions about the goals of the Mast Cell Connect registry, contact the study doctor at mastcellregistry@blueprintmedicines.com or at 617-714-6678.

Questions?

For questions about the goals of the Mast Cell Connect registry, contact the study doctor at mastcellregistry@blueprintmedicines.com or at 617-714-6678.

Questions?
Getting Involved

Who can join?
People with a diagnosis of mastocytosis, including systemic mastocytosis (SM), cutaneous mastocytosis (CM) and their variants, are invited to join Mast Cell Connect. To join, you must be able to provide informed consent. Anyone under 18, or adults who cannot make their own medical decisions or would prefer to have someone else enter their information, must have a family member, medical caregiver, legal guardian or other designee to register on their behalf.

What does participating in the registry involve?
If you join Mast Cell Connect, you will be asked to complete a questionnaire about your experience living with mastocytosis, as well as to share medical records that describe your diagnosis, treatments, symptoms and changes in the disease over time. You may occasionally be asked additional survey questions, and to ensure the registry’s accuracy, you will be asked to update your information a few times a year.

Who has access to Mast Cell Connect?
The broader medical community, including researchers, physicians, patient advocacy groups and companies engaged in mastocytosis research, can request access to the registry. All information in the registry is de-identified, meaning it has been stripped of information that could be used to identify you. As a participant, you have immediate access to the pool of de-identified survey answers.

Additional Resources

Here are more resources that you may find useful if you have mastocytosis, care for someone with mastocytosis, or would like to learn more about participating in clinical trials:

**Systemic Mastocytosis**
www.systemicmastocytosis.com

**The Mastocytosis Society**
www.tmsforacure.org

**National Organization for Rare Diseases (NORD): Mastocytosis**
www.rarediseases.org/rare-diseases/mastocytosis

**European Competence Network on Mastocytosis**
www.mastocytosis.eu

About the Sponsor

**About Blueprint Medicines**
Blueprint Medicines is a biotechnology company developing a new investigational treatment for systemic mastocytosis (SM). At Blueprint Medicines, we are motivated by one goal: to dramatically improve the lives of people with debilitating diseases. Our investigational therapies are currently in clinical studies for SM, gastrointestinal stromal tumors and hepatocellular carcinoma. 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
After Years of Planning...

The American Initiative in Mast Cell Diseases (AIM) is finally being launched! In collaboration with The Mastocytosis Society, Inc., a partnered Patient/Caregiver Conference was followed by an inaugural meeting of physicians and investigators in May 2019 at Stanford University School of Medicine. AIM will be a network of diagnosis, treatment and research centers established first across the United States and ultimately planned to encompass all of North, Central and South America. Please join us in celebrating this giant step toward improved care for our patient population and exciting new research initiatives in mast cell diseases. Visit www.aimcd.net for more information on AIM!

TMS Needs Your Help!

If you find the information and support provided by TMS helpful for you or your patients, please consider making a monetary contribution to our organization. Donations, easily made through our website, www.tmsforacure.org, help us fulfill our mission of Research, Education, Advocacy and Support for Mast Cell Diseases. TMS is an all-volunteer organization that receives funding directly from people affected by mast cell diseases. Any donation is appreciated!

The Mastocytosis Society, Inc. invites you to visit our exhibitor booths at the following Medical Conferences:

- American Academy of Pediatrics
- American Society of Hematology
- American Academy of Dermatology
- American Academy of Allergy, Asthma and Immunology

Physicians treating patients with mast cell disease, please self-enroll in our TMS physicians’ database: https://tmsforacure.org/physician-database/