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

The Mastocytosis Society, Inc. | 2020-2021 - Volume 24

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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.
Committees

Advanced Systemic Mastocytosis Variants
(advancedvariants@tmsforacure.org)
Valerie M. Slee, RN, BSN, Chair
Michele O. Kress, Smoldering SM Liaison

Drug Shortage
(drugshortage@tmsforacure.org)
Valerie M. Slee, RN, BSN, Co-Chair
Emily A. Menard, Co-Chair
Carlene Bartolotta RN, BSN

Education
(education@tmsforacure.org)
Gail Barbera, Chair

Fundraising
(fundraising@tmsforacure.org)
Courtney Rabb, Chair

International Mastocytosis & Mast Cell Diseases Committee
Gail Barbera, USA Representative
Jodylynn Bachiman, Website Design Committee

Media Relations
(mediarelations@tmsforacure.org)
Ariella Cohen, JD, Chair

Medical Conference Planning
(medicalconference@tmsforacure.org)
Kathy Tomasic
Chantelle Bosco, Materials Management

Patient Care Coordination
(nurses@tmsforacure.org)
Jan Hempstead, RN, Chair

Pediatric
(pediatrics@tmsforacure.org)
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Political and Patient Advocacy
(advocacy@tmsforacure.org)
Jennifer Lockhart, Chair

Research
(research@tmsforacure.org)
Susan Jennings, PhD, Chair

Support Groups
(supportgroups@tmsforacure.org)
Gail Barbera, Interim Support Group Chair
Jan Hempstead, RN Patient Care Coordination Chair
Emily Bolden, Interim Support Group Coordinator

Website Content
(education@tmsforacure.org)
Gail Barbera, Co-Chair
Susan Jennings, PhD, Co-Chair

SUPPORTING CONTRACTORS

Graphic Designers
Rachael Zinman
John Gilligan

Webmaster
(webmaster@tmsforacure.org)
Ben Rabb

Board of Directors

Executive Board/Officers
Valerie M. Slee RN, BSN: Chair
Medical Advisory Board Liaison
chairman@tmsforacure.org

Jan Hempstead, RN: Interim Vice Chair
Patient Care Coordination Chair
nurses@tmsforacure.org

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Education Chair
secretary@tmsforacure.org
education@tmsforacure.org

Rosemary Schultz: Interim Treasurer
treasurer@tmsforacure.org

Other Board Members/Directors
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fundraising@tmsforacure.org

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advocacy@tmsforacure.org

Rita Barlow: Retired, Director Emeritus

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.

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. 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. 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...
Overview, Definitions, Diagnosis and Classification
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dysautonomia and connective tissue disease. Although systemic mastocytosis is a rare disease,3 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 systematically 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 b:
• 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.
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. Over the last two decades, with development of improved methodology for identification of abnormal mast cells, it became apparent that there were patients who exhibited symptoms of mast cell mediator release who did not fulfill the criteria for SM. 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).

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, 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, pruritus (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.

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. The consensus article provides a method for calculating the required minimum rise in serum tryptase. 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, or its metabolite, 11β-prostaglandin-F, (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.

Finally, the third co-criterion requires a response (based on response criteria) to medications that inhibit the action of histamine. 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.

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References


### Cytology of Mast Cells

By Tracy I. George, MD

<table>
<thead>
<tr>
<th>Mast cell types</th>
<th>Morphology</th>
<th>Types of disease</th>
</tr>
</thead>
<tbody>
<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</td>
<td>Hypogranular, enlarged, with cytoplasmic projections</td>
<td>Indolent SM, ASM, SM-AHN</td>
</tr>
<tr>
<td>(spindle shaped)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical type II</td>
<td>Enlarged and round, hypogranular; indented bilobed nuclei</td>
<td>Mast cell leukemia, myelomastocytic leukemia</td>
</tr>
<tr>
<td>(promastocyte)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metachromatic blast</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>
<tr>
<td>(immature)</td>
<td></td>
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</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**

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).1,6

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 pruritis8
• 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

- 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

**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

**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 Mastocytosis8

<table>
<thead>
<tr>
<th>Variant</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ISM (Indolent systemic mastocytosis)</strong></td>
<td>WHO criteria for SM met, MC burden low, +/- skin lesions, no C findings, no evidence of AHN</td>
</tr>
<tr>
<td></td>
<td>• Bone marrow mastocytosis: ISM variant with BM involvement, but no skin lesions</td>
</tr>
<tr>
<td><strong>SSM (Smoldering systemic mastocytosis)</strong></td>
<td>WHO criteria for SM met, typically with skin lesions, with 2 or more B findings, but no C findings.</td>
</tr>
<tr>
<td><strong>Advanced Disease Variants</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SM-AHN (SM with an associated hematologic neoplasm, formerly SM-AHNMD)</strong></td>
<td>Meets criteria for SM and also criteria for an AHN (MDS, MPN, MDS/MPN, AML), or other WHO-defined myeloid hematologic neoplasm, +/- skin lesions.</td>
</tr>
<tr>
<td><strong>ASM (Aggressive systemic mastocytosis)</strong></td>
<td>Meets criteria for SM with one or more C findings. No evidence of MCL, +/- skin lesions.</td>
</tr>
<tr>
<td><strong>MCL (Mast cell leukemia)</strong></td>
<td>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: &lt; 10% of peripheral blood white cells are MCs. Usually without skin lesions.</td>
</tr>
</tbody>
</table>

*SM-AHN is the recently updated term from the 2016 WHO classification of mastocytosis;9 a lymphoproliferative disorder or plasma cell dyscrasia may rarely be diagnosed with SM. WHO: World Health Organization; BM: bone marrow; MC: mast cell; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; MDS/MPN: myelodysplastic syndrome/myeloproliferative neoplasm overlap disorders; AML: acute myeloid leukemia.
The majority of adult patients fit into this category, fulfilling the criteria for indolent systemic mastocytosis (ISM)\(^2\)\(^{-12}\). 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.

**INDOLENT SYSTEMIC MASTOCYTOSIS**

Isolated bone marrow mastocytosis (BMM) is a variant of indolent SM.\(^1\)\(^2\) BMM is characterized by the absence of skin lesions, lack of multi-organ involvement, and an increased incidence of anaphylaxis.\(^1\)\(^3\)

Well differentiated SM (WDSM) first described in 2004\(^1\)\(^4\), is reported in the literature as a rare variant that fulfills the major criterion for SM and continues to be studied by researchers.\(^1\)\(^5\)\(^{-17}\) 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.\(^1\)\(^7\) 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.\(^1\)\(^7\) 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.\(^1\)\(^6\)

Baseline serum tryptase levels

\(\text{Continued on page 14}\)

**Table 2. B and C Findings*\(^9\)**

<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 10^9/L, Hb &lt; 10 g/dL, or platelets &lt; 100 x 10^9/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 and/or splenomegaly on palpation without impairment of organ function and/or lymphadenopathy on palpation/imaging (&gt; 2 cm)</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: osteolyses 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.
Systemic Mastocytosis Variants

Continued from page 13

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\(^8\)**

**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.\(^8,19,20\) 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\(^21\)**

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 chronic\(^23\) 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.
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.

**SECONDARY MCAS**

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

**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. 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. Review of other causes of MCAS to aid physicians in evaluation for the exclusionary diagnosis of idiopathic MCAS have also been provided.

**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. 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. 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, 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.

If a patient responds well to anti-mediator treatment and fulfills the other proposed criteria, 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.

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. 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.

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, 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

**SYMPTOMS AND TRIGGERS OF MAST CELL ACTIVATION (MASTOCYTOSIS AND MCAS)**

**Mast Cell Activation and Triggers**

Mast cells can be activated to release mediators by multiple triggers. Possible triggers of mediator release are shown below in Figure 1. Please note that any patient with a mast cell disease can potentially react to any trigger, and triggers can change over the course of the disease. In addition, patients may experience reactions to virtually any medications, including medications that they have tolerated previously. Common medication reactions in mast cell disease patients include, but are not limited to: opioids, antibiotics, NSAIDs, alcohol-containing medicines and intravenous vancomycin. Use with caution. More information related to drug hypersensitivity in mast cell diseases is available in a position paper by European specialists (http://onlinelibrary.wiley.com/doi/10.1111/all.12617/full).

Signs, Symptoms And Triggers

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Fatigue</th>
<th>Food or beverages, including alcohol</th>
<th>Mechanical irritation, friction, vibration</th>
<th>Infections (viral, bacterial or fungal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat, cold or sudden temperature changes, Sun/sunlight</td>
<td>Stress: emotional, physical, including pain, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)</td>
<td>Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes</td>
<td>Natural odors, chemical odors, perfumes and scents</td>
<td>Venoms (bee, wasp, mixed vespid, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos and fleas, etc.)</td>
</tr>
</tbody>
</table>
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, gastroesophageal 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 roll 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 Mediators\(^15,16\)

<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 Symptoms\(^14,15\)

**MAST CELL MEDIATOR SYMPTOMS**

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

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 Plan\(^7\) and the Anaphylaxis Guidelines Pocketcard.\(^8\)

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)].

**References**


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:

\[
\text{(basal level, plus 20\%) + additional 2 ng/ml = the serum tryptase level, after a reaction, that must be met or exceeded in order to meet a rise in serum tryptase considered a mast cell activation event.}
\]

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.\(^5\), 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: \(^7\)

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Tests

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- 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 ant mediator 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

Routine and Follow-up Testing for MCAS

In patients who demonstrate a mediator rise, mediator testing should be repeated periodically. In addition, a complete blood count (CBC) with differential, blood chemistries, immunoglobulin levels, liver function tests, DEXA scans for bone density, and other testing may all be done as part of the routine exam, depending on the patient’s age, presenting symptoms, coexisting conditions and medication profile.8

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.1,9-12

KIT Mutation Testing13

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.14 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
found to have the \( \text{KIT} \) D816V mutation 92% of the time using the newer allele-specific qPCR blood test.\(^{14}\)

Although the more sensitive test for the \( \text{KIT} \) 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 \( \text{KIT} \) 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 \( \text{KIT} \) 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.\(^{13,15}\) If an adult with systemic mastocytosis does not test positive for the \( \text{KIT} \) D816V mutation using sensitive testing methods, then sequencing of \( \text{KIT} \) might be considered.

Knowing the \( \text{KIT} \) 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 \( \text{KIT} \) testing more widely available in the near future. More information on the use of \( \text{KIT} \) 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:\(^{13}\)

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

**Diagnostic Workup for Advanced Systemic Mastocytosis Variants or Associated Hematological Disorders\(^{1,13,16,17}\)**

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:

- Serum tryptase and 24-hour or spot urines for N-methyl histamine, prostaglandin D2 (PGD2), 11\( \beta \)-prostaglandin \( F_2\alpha \)
- 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 \( \text{KIT} \) D816V mutation in peripheral blood/bone marrow, if not already performed; \( \text{KIT} \) sequencing, if indicated\(^{13}\)
- 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.

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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.**

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

References


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

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.

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
• **Other medications may include**: omalizumab (Xolair®, anti-IgE therapy), steroids, and proton pump therapy *(for additional control of gastroesophageal reflux (GERD), but proton pump therapy may not replace the H2 antihistamine necessary to stabilize mast cells)*

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>Chlorpheniramine</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>Loratidine</td>
</tr>
<tr>
<td>Clarinex®</td>
<td>Desloratidine</td>
</tr>
<tr>
<td>Zaditor®/Zaditen® <em>(in Europe)</em></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
Medications To Treat Mast Cell Diseases
Continued from page 27

Table 4. Mast Cell Stabilizers and Others

<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, acetylsalicylic acid (for those with high prostaglandin levels; aspirin therapy must be initiated under the direct supervision of a physician!)</td>
</tr>
<tr>
<td>Xolair®</td>
<td>Omalizumab</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 Mastocytosis

<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 should either be performed with the greatest 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.

**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. 
  - No race has been found to be predominant.
- 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**
- 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

**Maculopapular Cutaneous Mastocytosis (MPCM)/Urticaria Pigmentosa (UP)**
- Red maculopapular lesions tend to wheal when scratched (positive Darier’s sign)
- Blister formation can occur with rubbing or stroking of lesion and is associated with pruritis
- 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 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.

*Continued on page 32*
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.\(^2\), \(^10\)

- 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)\(^12\) to ant mediator 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 by Gene By Gene (Tryptase CNV test).

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 vespids, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos 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 ant mediator therapy when indicated and always carry two doses of injectable epinephrine.

*Continued on page 34*
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

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 rashes
  - 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

- **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

- **Gynecological**
  - uterine cramps
  - bleeding

- **Urinary**
  - bladder irritability
  - frequent voiding

- **Systemic and/or Organ Specific**
  - anaphylaxis
  - angioedema (swelling)

Symptoms can be 
Sudden and 
Unpredictable in onset

Patients may have a few or many symptoms

Learn more at tmsforacure.org

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

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

**UNITED STATES OF AMERICA**

**Alabama**

University of Alabama at Birmingham
UAB Comprehensive Cancer Center
1720 2nd Avenue, South
North Pavilion, Room 2540C
Birmingham, AL 35294

Contact: Pankit Vachhani, MD
Email: pvachhani@uabmc.edu
Phone: 205-934-6770

Specialization: Adults with SM, SSM, ASM, SM-AHN and MCL.

**California**

Stanford Cancer Center
875 Blake Wilbur Drive, Room 2327B
Stanford, CA 94305-5821

Contact: Jason Gotlib, MD, MS
Professor of Medicine (Hematology)
Stanford University Medical Center
Email: jason.gotlib@stanford.edu
Phone: 650-498-6000
Fax: 650-724-5203

Specialization: Adults. Biopsy-proven, advanced variants of SM only, including SSM, SM-AHN, ASM and MCL. Diagnosis, treatment, and research.

**Colorado**

University of Colorado Hospital
Blood Cancer/Bone Marrow Transplant Program
1665 Aurora Ct, Rm 2257
Aurora, CO 80045

Contact: William A. Robinson, MD, PhD
Professor, Division of Medical Oncology
Email: William.Robinson@ucdenver.edu
Phone: 720-848-2869
Fax: 720-848-0704

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

**Illinois**

Rush University
Department of Medicine
Division of Hematology, Oncology and Cell Therapy
1725 West Harrison St., Suite 836
Chicago, IL 60612
888-352-7874 (appointment line)

Contact: Celalettin Ustun, MD
Email: celalettin_ustun@rush.edu

Specialization: Adults with advanced variants: SSM, ASM, SM-AHN, and MCL. Diagnosis, treatment, and research. Stem cell transplant program.

**Maryland**

National Institutes of Health/
National Institute of Allergy and Infectious Diseases (NIH/NIAMID)
Building 10, Room 11C207
10 Center Drive - MSC1881
Bethesda, MD 20814-1881

Contact: Dean D. Metcalfe, MD
Chief, Mast Cell Biology Section
Email: dmetcalfe@niaid.nih.gov
Phone: 301-496-2165
Fax: 301-480-8384

**Massachusetts**

Brigham and Women’s Hospital (BWH) and Dana Farber Cancer Institute (DFCI): Boston Center of Excellence for Mastocytosis

Brigham and Women’s Hospital
Division of Rheumatology, Immunology and Allergy
60 Fenwood Rd., Brookline, MA 02115
Phone: 617-732-9850
Fax: 617-525-1310

Contact: Mariana Castells, MD, PhD
Director, Center of Excellence for Mastocytosis
Professor of Medicine
Harvard Medical School
Email: mcastells@partners.org
Phone: 617-732-9850
Fax: 617-525-1310

Contact: Richard Horan, MD
Assistant Professor of Medicine
Harvard Medical School
Email: rhoran@partners.org
Phone: 617-732-9850
Fax: 617-525-1310
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: 507-284-3077
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.

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

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

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.

Michigan
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.

Continued on page 42

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Medical & Research Centers that Treat Patients with Mast Cell Diseases

Continued from page 41

**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 Clínicas, University of São Paulo,
São Paulo, BRAZIL
**Contact:** Pedro Giavina-Bianchi Jr., MD, PhD
Head of Allergy and Immunology Service
Associate Professor
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
Clinical Associate Professor
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.

Ivan Alvarez-Twose, MD
Staff Physician and Clinical Coordinator,
Instituto de Estudios de Mastocitosis de Castilla La Mancha (CLMast)
Toledo, Spain
Email: ivana@sescam.jccm.es
Phone: 0034-615-653-157

K. Frank Austen, MD (Honorary)
Astra Zeneca Professor of Respiratory and Inflammatory Diseases
Department of Medicine Brigham and Women’s Hospital
Smith Building, Room 638
One Jimmy Fund Way
Boston, MA 02115
Email: fausten@rics.bwh.harvard.edu
Phone: 617-525-1300
Fax: 617-525-1310

Patrizia Bonadonna, MD
Allergy and Immunology Clinic
Multidisciplinary Outpatient Clinic of Mastocytosis (also hymenoptera venom allergy, drug allergy and other allergic diseases)
Verona General and University Hospital
Piazzale Stefani 1
Verona, Italy
Email: patrizia.bonadonna@ospedaleuniverona.it
Phone: +390458122556
Fax: +390458122048

Joseph Butterfield, MD
Co-Director, Mayo Clinic Program for Mast Cell and Eosinophil Disorders
W15-B Mayo Clinic 200 SW 1st Street
Rochester, MN 55905
Email: butterfield.joseph@mayo.edu
Phone: 507-284-9077
Fax: 507-284-0902

Mariana Castells, MD, PhD
Professor of Medicine
Harvard Medical School
Director, Mastocytosis Center of Excellence
Brigham and Women’s Hospital
Allergy and Clinical Immunology
60 Fenwood Rd., Brookline, MA 02115
Email: mcastells@partners.org
Phone: 617-732-9850
Fax: 617-525-1310

Madeleine Duvic, MD
Professor and Deputy Chair, Dermatology,
Univ. of Texas MD Anderson Cancer Center
1515 Holcombe Blvd, Unit 1452
Houston, TX 77030
Email: mduvic@mdanderson.org
Phone: 713 745-4615
Fax: 713 745-3597

Luis Escrivanó, MD, PhD
Coordinator, Spanish Network on Mastocytosis (REMA) Associated Research, Servicio de Citometría, Centro de Investigación del Cáncer, Universidad de Salamanca
Salamanca, Spain
Email: escribanomoraluis@gmail.com

Tracy I. George, MD
Professor of Pathology
University of Utah
Executive Director, Clinical Trials and PharmaDx
Medical Director, Hematopathology
ARUP Laboratories
500 Chipeta Way
Salt Lake City, UT 84108
Email: tracy.george@aruplab.com
Phone: 801-583-2787
Fax: 801-584-5124

Jason Gotlib, MD, MS
Associate Professor of Medicine (Hematology), Director, Stanford Hematology Fellowship Program Director, MPN Center
Stanford Cancer Institute
875 Blake Wilbur Drive, Room 2324
Stanford, CA 94305-5821
Email: jason.gotlib@stanford.edu
Phone: 650-725-0744
Fax: 650-724-520

Norton J. Greenberger, MD (Honorary)
Clinical Professor of Medicine/Gastroenterology
Harvard Medical School
Email: ngreenberger@partners.org

Continued on page 44
<table>
<thead>
<tr>
<th>Medical Advisory Board</th>
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<tbody>
<tr>
<td>Matthew J. Hamilton, MD</td>
</tr>
<tr>
<td>Assistant Professor of Medicine</td>
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<tr>
<td>Harvard Medical School</td>
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<tr>
<td>Division of Gastroenterology</td>
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<tr>
<td>Brigham and Women’s Hospital</td>
</tr>
<tr>
<td>75 Francis St.</td>
</tr>
<tr>
<td>Boston, MA 02115</td>
</tr>
<tr>
<td>Email: <a href="mailto:mjhamilton@partners.org">mjhamilton@partners.org</a></td>
</tr>
<tr>
<td>Phone: 617-732-6389</td>
</tr>
<tr>
<td>Fax: 617-566-0338</td>
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<tr>
<td>Olivier Hermine, MD, PhD</td>
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<tr>
<td>Université Sorbonne Paris Cité</td>
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<tr>
<td>Department of Clinical Hematology</td>
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<td>National Center of Mastocytosis</td>
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<tr>
<td>Hôpital Necker</td>
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<tr>
<td>149-161 Rue de Sèvres,</td>
</tr>
<tr>
<td>75015 Paris, France</td>
</tr>
<tr>
<td>Email: <a href="mailto:ohermine@gmail.com">ohermine@gmail.com</a></td>
</tr>
<tr>
<td>Tel: 33-1-44-49-52-82 (office)</td>
</tr>
<tr>
<td>Nicholas Kounis, MD, PhD</td>
</tr>
<tr>
<td>Patras Highest Institute of Education and Technology</td>
</tr>
<tr>
<td>Professor of Medicine in Cardiology</td>
</tr>
<tr>
<td>Department of Medical Sciences</td>
</tr>
<tr>
<td>7 Aratou St.</td>
</tr>
<tr>
<td>Queen Olga’s Square</td>
</tr>
<tr>
<td>Patras 26221, Greece</td>
</tr>
<tr>
<td>Email: <a href="mailto:ngkounis@otenet.gr">ngkounis@otenet.gr</a></td>
</tr>
<tr>
<td>Phone: +302610279579</td>
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<td>Fax: +302610279579</td>
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<tr>
<td>Anne Maitland, MD, PhD</td>
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<td>Anne Maitland, MD, PhD</td>
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<tr>
<td>Asst. Professor, Dept. of Medicine - Allergy &amp; Clinical Immunology</td>
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<tr>
<td>Icahn School of Medicine at Mount Sinai</td>
</tr>
<tr>
<td>New York, NY 10029</td>
</tr>
<tr>
<td>Medical Director, Comprehensive Allergy &amp; Asthma Care, PLLC</td>
</tr>
<tr>
<td>200 South Broadway, Suite 104</td>
</tr>
<tr>
<td>Tarrytown, NY 10591</td>
</tr>
<tr>
<td>Email: <a href="mailto:anne.maitland@mssm.edu">anne.maitland@mssm.edu</a></td>
</tr>
<tr>
<td>Phone: 914-631-3283</td>
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<td>Fax: 914-337-8204</td>
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<tr>
<td>Larry Schwartz, MD, PhD</td>
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<td>Professor of Medicine</td>
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<td>Chair, Division of Rheumatology, Allergy, and Immunology</td>
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<td>Virginia Commonwealth University</td>
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<td>P.O. Box 980263</td>
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<td>1250 East Marshall St.,</td>
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<td>Richmond, VA 23298</td>
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<td>Email: <a href="mailto:lbschwar@vcu.edu">lbschwar@vcu.edu</a></td>
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<td>Phone: 804-828-9685</td>
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<td>Fax: 804-828-0283</td>
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<tr>
<td>Theoharis Theoharides, MD, PhD</td>
</tr>
<tr>
<td>Professor of Pharmacology and Internal Medicine</td>
</tr>
<tr>
<td>Tufts University School of Medicine</td>
</tr>
<tr>
<td>136 Harrison Avenue</td>
</tr>
<tr>
<td>Boston, MA 02111</td>
</tr>
<tr>
<td>Email: <a href="mailto:Theoharis.Theoharides@Tufts.edu">Theoharis.Theoharides@Tufts.edu</a></td>
</tr>
<tr>
<td>Phone: 617-636-6866</td>
</tr>
<tr>
<td>Fax: 617-636-2456</td>
</tr>
<tr>
<td>Megha M. Tollefson, MD</td>
</tr>
<tr>
<td>Assistant Professor of Dermatology and Pediatrics</td>
</tr>
<tr>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>200 First Street SW</td>
</tr>
<tr>
<td>Rochester, MN 55905</td>
</tr>
<tr>
<td>Email: <a href="mailto:Tollefson.Megha@mayo.edu">Tollefson.Megha@mayo.edu</a></td>
</tr>
<tr>
<td>Phone: (507) 284-3579</td>
</tr>
<tr>
<td>Fax: (507) 284-2072</td>
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<tr>
<td>Celalettin Ustun, MD</td>
</tr>
<tr>
<td>Rush University</td>
</tr>
<tr>
<td>Department of Medicine</td>
</tr>
<tr>
<td>Division of Hematology, Oncology and Cell Therapy</td>
</tr>
<tr>
<td>1725 West Harrison St., Suite 836</td>
</tr>
<tr>
<td>Chicago, IL 60612</td>
</tr>
<tr>
<td>Phone: 888-352-7874 (appointment line)</td>
</tr>
<tr>
<td>Email: <a href="mailto:cealettin_ustun@rush.edu">cealettin_ustun@rush.edu</a></td>
</tr>
<tr>
<td>Peter Valent, MD</td>
</tr>
<tr>
<td>Department of Internal Medicine I</td>
</tr>
<tr>
<td>Division of Hematology and Hemostaseology</td>
</tr>
<tr>
<td>University of Vienna</td>
</tr>
<tr>
<td>Währinger Gürtel 18-20</td>
</tr>
<tr>
<td>A-1090 Vienna, Austria</td>
</tr>
<tr>
<td>Email: <a href="mailto:peter.valent@meduniwien.ac.at">peter.valent@meduniwien.ac.at</a></td>
</tr>
<tr>
<td>Phone: +43 1 40400-5488 or -6086</td>
</tr>
<tr>
<td>Fax: +43 1 40400 4030</td>
</tr>
<tr>
<td>Srdan Verstovsek, MD, PhD</td>
</tr>
<tr>
<td>Professor</td>
</tr>
<tr>
<td>Leukemia Department</td>
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<tr>
<td>MD Anderson Cancer Center</td>
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<tr>
<td>1515 Holcombe Blvd, Unit 428</td>
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<tr>
<td>Houston, TX 77030</td>
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<tr>
<td>Email: <a href="mailto:sverstov@mdanderson.org">sverstov@mdanderson.org</a></td>
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<tr>
<td>Phone: 713-792-7305</td>
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<td>Fax: 713-794-4297</td>
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</table>
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.
Together, we can advance mastocytosis research.

What Is Mast Cell Connect?

Mastocytosis is a rare disease in which immune cells known as mast cells abnormally build up in the skin, known as mastocytosis or CM (cutaneous mastocytosis), or in other organs such as the spleen and the gastrointestinal tract (known as systemic mastocytosis or SM). Today, mastocytosis is recognized as a disease. It is a voluntary online registry created to advance the understanding of mastocytosis and the more people who have mastocytosis and the more people participate in research and clinical studies.

Who can join?

People with a diagnosis of mastocytosis, including those with systemic mastocytosis (SM), cutaneous mastocytosis, or SM.

Who has access to Mast Cell Connect?

Information is de-identified and can be used to identify you. As a participant, you could be used to identify you. As a participant, you have immediate access to the pool of de-identified data collection tool. Those who participate in Mast Cell Connect will be able to view the de-identified summary information from patients with mastocytosis on their experiences with the disease. The ultimate goal of Mast Cell Connect is to advance the understanding of mastocytosis.

What questions does Mast Cell Connect answer?

For questions about the goals of the mast cell registries have proven to be a valuable tool in better understanding rare diseases like mastocytosis.

Additional Resources

- The Mastocytosis Society: http://www.systemicmastocytosis.com
- National Organization for Rare Diseases (NORD): http://www.rarediseases.org/rare-diseases/mastocytosis
- Mast Cell Connect is an electronic patient registry designed to advance research and connect patients with researchers, and to choose to participate in other related research studies.

Questions?

- For all other questions, contact the Mast Cell registry coordinator at coordinator@mastcellconnect.org. 617-714-6678.
- mastocytosis research due to limited treatment options, and there is no cure.
- In patients with mastocytosis, mast cells can accumulate widely, but in more severe cases, mast-cell accumulation in the organs results in organ dysfunction. In these cases, the symptoms and severity of mastocytosis can vary widely.

The signs, symptoms, and severity of mastocytosis vary widely. The symptoms of mastocytosis and quality of life can be significantly impacted by disease. In mastocytosis, the abnormal growth of mast cells produce so-called mediators, like histamine, that help activate the immune system and cause flushing, shortness of breath and anaphylactic shock.

The signs, symptoms and severity of mastocytosis vary widely. In mastocytosis, abnormal growth of mast cells produce so-called mediators, like histamine, that help activate the immune system and cause symptoms that resemble allergies, including hives, cause symptoms that resemble allergies, including hives.

In patients with mastocytosis, mast cells lead to high levels of these mediators, and can cause flushing, shortness of breath and anaphylactic shock.

In patients with mastocytosis, mast cells lead to high levels of these mediators, and can cause flushing, shortness of breath and anaphylactic shock.

Mast cell research needs your help to answer the question: What is the best treatment for people with mastocytosis?

Mast cell research needs your help to answer the question: What is the best treatment for people with mastocytosis?
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:

- **Together with Systemic Mastocytosis**
  - [www.systemicmastocytosis.com](http://www.systemicmastocytosis.com)

- **The Mastocytosis Society**
  - [www.tmsforacure.org](http://www.tmsforacure.org)

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

- **European Competence Network on Mastocytosis**
  - [www.mastocytosis.eu](http://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](http://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](http://www.patientcrossroads.com).

Sponsored by Patient Crossroads™

Learn from other patients’ experiences.
By participating, you will gain access to data and insights gleaned from other patients’ responses that may be useful in better understanding your own disease.

Find out about clinical trials and other research studies. You can sign up to be notified about clinical trials and other research studies that you may be eligible for based on the information you enter into the registry.

Advance research and speed development of new treatments. By improving our understanding of mastocytosis and its impact on patients over time, you can help spur the development of new potential treatments.
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/