

The Mastocytosis Society, Inc.

Pediatric Mast Cell Disorders: Facts in Brief

By Valerie M. Slee, RN, BSN, Mishele Cunningham, RN, BSN, PHN, and Susan Jennings, PhD

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Pediatric mast cell disorders, a group of rare diseases, are characterized by either the presence of too many mast cells in the skin or other tissues (pediatric mastocytosis),¹ or recurrent symptoms arising from release of mast cell mediators in two or more organ systems, in parallel (mast cell activation syndrome, MCAS). Mast cells are instrumental in mediating anaphylaxis, and children with mast cell disorders are at higher risk to develop both provoked and unprovoked episodes of anaphylaxis. A child whose disease appears to be confined to the skin may still exhibit systemic symptoms due to mast cell activation and mediator release.²

Symptoms common to pediatric mastocytosis and MCAS include flushing of the face and neck, dermatographism, gastrointestinal complaints [such as diarrhea, abdominal pain, nausea, gastroesophageal reflux (GERD)], pruritis, dyspnea, headache, lethargy, fatigue, and neuropsychiatric symptoms. Many children with these disorders 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, some will go on to be diagnosed as indolent systemic mastocytosis (ISM) and some will evolve into well-differentiated systemic mastocytosis (WDSM).²

DEFINITIONS^{1, 3}

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.

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.⁴
 - No race has been found to be predominant.⁵
- 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 Mastocytoma¹

- 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 WDSM²

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

- Red maculopapular lesions tend to wheal when scratched (positive Darier's sign)
- Blister formation can occur with rubbing or stroking of lesion and is associated with pruritis⁵

- Encompasses several clinical entities with different outcomes, including: pitted melanotic macules, reddish brown telangiectatic macules, lightly pigmented papules, brownish papules, and small nodules
- This group is divided into two sub-variants
 - Monomorphic variant (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)¹

- Skin thickened, hyperpigmented and diffusely infiltrated
- Can involve up to 100% of the skin with the trunk, head and scalp heavily affected
- Can appear at birth or early infancy; may persist into adulthood, possibly as well differentiated systemic mastocytosis (WDSM)²
- 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, and can be indicative of WDSM²

SYMPTOMS OF MAST CELL ACTIVATION Which May be Seen in Both Pediatric CM and MCAS⁶

- 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 CM

- 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:
 - abnormal peripheral blood counts, organomegaly, significant lymphadenopathy, severe recurrent systemic mast cell mediator-related symptoms, persistent high tryptase, persistence of disease into adulthood^{5, 7}

Pediatric MCAS

- Although specific guidelines do not exist for diagnosing pediatric MCAS, proposed consensus criteria for diagnosing MCAS have been utilized by specialists.⁸
- 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.⁸
 - 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 of the three urinary mediators, n-methyl histamine, prostaglandin-D₂, or its metabolite, 11β-prostaglandin-F_{2α} (24-hour urine test for any of the three, also best captured after a symptomatic episode).⁸ Additionally, Mayo Clinic (Rochester) has a test available to measure urinary levels of leukotrienes that is not yet

incorporated into this criteria, as it is not yet widely available. "It requires further study to determine if all patients with MCAS will demonstrate a rise in one of the known mast cell mediators for which tests are available."⁶

- The consensus article provides a method for calculating the required minimum rise in serum tryptase.⁸ 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:

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

(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 criteria⁹) to antimediator therapy.⁸

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
- Contrast dyes and medications, including: opioid narcotics, alcohol as an additive or in any form, IV vancomycin, neomycin, benzocaine, and certain anesthetics.¹⁰ See [TMS Emergency Protocol](#).
- 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 CM AND MCAS

- 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 pediatric CM only)
- Mast cell stabilizers
 - Oral cromolyn sodium
 - Ketotifen
- Injectable epinephrine
 - EpiPen®/EpiPen Jr® auto injector
- Topical treatments
 - Steroid creams
 - Cromolyn sodium cream 1%-5%
- No chemotherapy is indicated in cutaneous or indolent systemic mastocytosis in children, unless evidence of progression to aggressive disease is identified

PROGNOSIS

Pediatric CM

- Benign course will be seen in approximately 70% of patients.²
- Approximately 30% of pediatric mastocytosis cases persist into adulthood.²
- Children with extensive bullous lesions appear to be at increased risk of shock or sudden death from anaphylaxis.¹¹
- 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.¹¹

Pediatric MCAS

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

SUPPORT SERVICES

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

- The Mastocytosis Society, Inc. coordinates [support groups](#) in nearly every state.
- [Mastokids.org](#) is a site where parents and caregivers of children with mastocytosis or mast cell disease can come to learn, find support, and discover a safe environment to interact with other families.

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