Mastocytosis and Mast Cell Activation Syndrome (MCAS)

Mast cells (MC’s) are hematopoietic cells that are clonally increased in patients with mastocytosis. In cutaneous mastocytosis, the predominant form in children, mast cell infiltration is limited to the skin. In systemic mastocytosis (SM) there is organ infiltration by clonal MC’s that may or may not include the skin. Mast cell activation syndrome may present with symptoms similar to indolent systemic mastocytosis.

Systemic Mastocytosis: Symptoms and Signs. There may be marked variability from patient to patient. Gastrointestinal complaints (ascites, splenomegaly, bleeding, abdominal pain, diarrhea, malabsorption, nausea, vomiting, GERD, peptic ulcer disease); Dermatologic symptoms (urticaria pigmentosa (UP), telengiectasia macularis eruptiva perstans (TMEP), pruritus, flushing, bullous changes, angioedema); Cardiovascular symptoms (persistent tachycardia, chest pain, hypotension, syncope); Neurologic complaints (headache, dizziness, seizures, neuropsychiatric complaints, memory problems); Systemic symptoms (Mast cell activation “spells”, (pre)syncope, or anaphylaxis).

Systemic Mastocytosis-Classification. There are 4 variants: Indolent SM (ISM): The most frequent variant has normal life expectancy in most cases. Mediator blockade therapy is indicated. Cytoreductive therapy (e.g. interferon alpha 2b) is debated in some cases with disabling symptoms such as frequent anaphylaxis. SM associated with a clonal hematologic non-mast cell lineage disease (SM-AHNMD)-a myeloproliferative, myelodysplastic, or lymphoproliferative disorder (less common) is also found along with SM. Each disorder must be treated individually and prognosis depends on the associated hematologic disorder. Aggressive SM (ASM) Here findings of organ damage by mast cells predominate including cytopenias, ascites, malabsorption, or large osteolytic lesions. Cytoreductive treatment is often necessary. Mast Cell leukemia (MCL)-a rare form of mastocytosis has poor prognosis. (Mast cell sarcoma is a locally invasive tumor and may not meet criteria for SM.)

Systemic Mastocytosis-Formal Definition. The WHO definition for SM requires the presence of one major and one minor criterion or the presence of 3 minor criteria defined as follows: Major Criterion Multifocal dense infiltrates of MCs (>15 MCs per aggregate) in tryptase-stained biopsy sections of the bone marrow or of another extracutaneous organs. Minor Criteria 1. More than 25% of MC’s in bone marrow or other extracutaneous organ(s) show abnormal morphology in multifocal lesions on histologic examination. 2. KIT mutation at codon 816 (Asp816Val in most cases) in extracutaneous organ(s) (in most cases, bone marrow cells are examined). 3 KIT (+) MCs in bone marrow show aberrant expression of CD25. 4. Total serum tryptase >20 ng/mL.

Cutaneous mastocytosis Cutaneous mastocytosis is the most common form of mastocytosis found in children. In addition, the finding of cutaneous lesions of mastocytosis is common in the adult form of SM, whereas in children with cutaneous mastocytosis, complete resolution of the lesions is observed in over 50-70% of children by age 21; it is unusual for the cutaneous lesions to resolve in the adult form of SM. The skin lesions of patients with mastocytosis commonly show dermatographism and maculopapular hyperpigmented lesions that urticate when stroked (Darier’s sign).

Pediatric-Onset Mastocytosis Children with mastocytosis present predominately with cutaneous disease and UP is the most common presentation with a usual onset before age 2 years. These lesions usually persist and may be associated blistering, itching, hives, and/or flushing. The lesions may also
increase in number in early childhood. Children with the onset of disease in late childhood or adolescence may have indolent systemic disease however; patients with systemic disease may also present in infancy. It is common for children with cutaneous disease only to have mast cell-mediator symptoms with skin and GI symptoms being the most common. Serum tryptase may be elevated in all cutaneous variants. UP typically has the lowest range. Diffuse cutaneous mastocytosis (DCM) and mastocytoma tryptase levels are more reflective of skin mast cell burden, whereas in ISM reflect total mast cell burden.

**Mast Cell Activation Syndrome (MCAS)** Three criteria are required: 1) Patients exhibit two or more symptoms/organ involvement consistent with mast cell activation; 2) One or more mast cell mediator levels are elevated either at baseline or during acute episodes; 3) Clinical improvement occurs with medications that block the production of or action of mast cell mediators. MCAS may also be seen in three circumstances: 1) In patients who meet only one or two criteria of SM. These patients are felt to have an abnormal clone of mast cells and the disorder is termed “monoclonal” mast cell activation syndrome (either termed MMAS or MMCAS); 2) In patients with SM who undergo a mast cell degranulation event but when the primary diagnosis is SM; 3) Patients without SM or MMAS who meet the criteria of idiopathic anaphylaxis. It requires further study to determine if all patients with MCAS will demonstrate a rise in one of the known MC mediators for which tests are available.

**Treatment** Basic treatment for SM or MCAS can include H1 and H2 antihistamines, sodium cromolyn, a LTE4 receptor antagonist, and aspirin, if tolerated. Avoidance of common mast cell degranulating agents may prevent the need for medications. Note that not all of the listed triggers will produce reactions in all individuals. **Medications:** Codeine and narcotic analgesics; polymyxin B, dextran, NSAIDS, muscle relaxants, sympathomimetics, thiamine, amphotericin B, radiocontrast dyes. **Physical stimuli:** Heat; temperature change; friction; sunlight; environmental odors; **Known food and inhalant allergens.**  **Emotional Factors:** Stress; anxiety; depression. **Venoms:** Stinging insects; fire ants; snakes. **Alcoholic beverages:** Red or white wine.

**Medical Emergency Response Plan for Systemic Mastocytosis, Mast Cell Activation, and Anaphylaxis** •A treatment plan taking into account individual tolerance and effect of these medications should be developed for each patient by their physician. **Epinephrine** 0.3 cc of 1/1000 (0.3 mg) and repeat 3x at 5-minute intervals if BP < 90 systolic (0.15 cc for children under 12 years/<30 kg). Call 911 and take the patient to the closest Emergency Room after the first dose of epinephrine. **Diphenhydramine** 25-50 mg (12.5-25 mg for children under 12) orally, intramuscular or intravenously every 2-4 hours. **100% oxygen** by mask or nasal canula. Albuterol nebulization for bronchospasm or wheezing.

**Mastocytosis Centers** : Brigham & Women’s Hospital /Dana Farber Cancer Institute, Boston, MA.; Mayo Clinic Program for Mast Cell and Eosinophil Disorders, Rochester, MN; National Institutes of Health, Bethesda, MD; Stanford University, Palo Alto, CA; Virginia Commonwealth University, Richmond, VA; MD Anderson Hospital, Houston, TX; University of Utah, Salt Lake City, UT

**Support Groups** Support, education and research are provided through The Mastocytosis Society, Inc. (TMS) in the US. TMS, with its web site [www.tmsforacure.org.] and quarterly newsletter, also sponsors an annual meeting open to all patients with mast cell disorders and their families.

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