A Practical Approach to Cutaneous Mastocytosis in Children

Aimee Smidt, MD, FAAD, FAAP
Chair, Department of Dermatology
Associate Professor, Depts. of Dermatology & Pediatrics
University of New Mexico School of Medicine

AAD F072 - The Big C's: Children, Cancer, and Cutaneous Complications
February 2018

No Conflicts of Interest to Declare
This toddler girl is referred from her pediatrician for evaluation of numerous new “spots” over the last few months. Mom thinks they itch but isn’t sure. You:

A) Recommend monitoring for ABCDEs of melanoma surveillance, but these nevi appear normal

B) Biopsy for diagnostic purposes

C) Scratch one of them vigorously for diagnostic purposes

D) Start scratching yourself because this is highly contagious
History of Pediatric Mast Cell Disorders

- 1869 Nettleship/Tay described case of likely Urticaria Pigmentosa
- 1894 Unna identified ↑ mast cells in skin lesions
- 1949 Ellis pediatric autopsy – systemic mast cell infiltrates
Mast Cell Biology

- Develop from CD34+ KIT+ CD13+ multipotent hematopoietic marrow precursor cells
- Mature after reaching tissue (skin, mucosa)
- Often near vessels, including in brain
- Most prominent in respiratory, GI tract, skin, lymphoid tissue
- Function not completely understood
- Originally likely integral for parasitic defense
- Also participate in immune response to bacteria, viruses, dsRNA
- Role in both innate and adaptive immunity
Mast Cell Histology and Function

• Stain with Geimsa or toluidine blue shows characteristic metachromatic granules

• Contain vasoactive & proinflammatory mediators

• Substances secreted after IgE-receptor crosslinking by allergens/stimuli
Mast Cell Preformed Mediators

- Histamine
- Tryptase
- Chymase (variable)
- Heparin
- (Cathepsin G)
- Serotonin
- Additional chemokines, cytokines, GFs, etc

Subtypes based on expression of above:
- Skin: both Tryptase & Chymase
- Organ mucosa: Tryptase, little/no Chymase
- Minor: express Cathepsin G

Mast cells responsible for most histamine found in normal tissues (except CNS, UGI)
Mast Cell: Maturation and T-cell Activation

- 4 Phases:
  - Non-granulated blast cell
  - Metachromatic blast cell
  - Promastocyte (aka Atypical mast cell type II)
    - Bi-/multilobed monocytoid nuclei
  - Mature mast cell

- Immature types seen in more severe forms of SM

After T-cell Activation:
- Synthesize Lipid Mediators:
  - Lipoxygenase
  - Prostaglandin D2, E2
  - Leukotriene B4, C4
  - Platelet-activating factor

- Produce Chemokines, Cytokines, GFs:
  - IL1, 5, 6, 13, 16, 18
  - TGFβ, TNFa
  - M-CSF, bFGF, VEGF, PDGF, Stem cell factor
    - Binds (KIT)(CD117) → Activate/differentiation mast cells
Mast Cells gone wrong...

- Disease due to:
  - Excessive mast cell burden
  - Constitutively released mediators

- Disruption normal function of chemokines, cytokines, GFs/GFRs →
  - Aberrant development
  - Uncontrolled proliferation
Prevalence & Genetics

- Approx 1/1000 Derm visits (↑in Peds Derm)
- C-KIT codon 816 mutation (D816V substitution)
- C-KIT = Proto-oncogene, transmembrane tyrosine kinase receptor
- Adult mutation → SCF-independent autophosphorylation & cell growth
- Traditionally thought that most pediatric pts LACK c-KIT codon 816 mutations
- But pediatric pts may show other c-KIT mutations...
  - N=50, analysis of entire c-KIT sequence
  - 44% outside exon 17 (exon 8,9)
  - 42% exon 17
  - Somatic, constitutive activation
  - No geno/phenotype correlation
  - Unclear familial vs spontaneous
- Unclear why pediatric disease acts differently, even w same mutation, but now many mutations recognized
WHO Classification
(More relevant in adults)

- **Cutaneous Mastocytosis**
  - Maculopapular type (Urticaria Pigmentosa) *(most common; best prognosis)*
  - Diffuse cutaneous mastocytosis
  - Solitary mastocytosis/mastocytoma

- Indolent systemic mastocytosis *(good prognosis)*
  - Multifocal marrow/organ involvement, atypical MC, etc

- Systemic mastocytosis in association w clonal hematological non-mast cell lineage disease *(variable prognosis)*

- Aggressive systemic mastocytosis *(poor prognosis)*

- Mast cell leukemia (MCL) *(poor prognosis)*

- Mast cell sarcoma *(poor prognosis)*

- Extracutaneous mastocytosis *(good prognosis-rare)*
“Solitary” Mastocytoma

- Young infants/children, not usually truly congenital

- Yellow-reddish tan nodule or plaque (can be grouped, i.e. not truly “solitary”)

- Diff Dx: Histiocytosis, melanocytic, xanthoma (JXG), smooth muscle hamartoma, cutaneous leukemia/lymphoma, other dermal tumors

- Darier sign often diagnostic

- Path (if done): Dense aggregates of mature mast cells without atypia

- Resolve spontaneously over years time
“Darier’s Sign”

- Vigorous rubbing/scratching with tongue depressor or back of thumbnail x 10-15 seconds

- Over minutes, produces localized:
  - Erythema
  - Edema
  - Peau d’orange change
  - Vesiculation/Bulla formation
  - Petechiae (Heparin...)

- If you expect positive, sometimes just need to wait 5-10+ minutes

- Sometimes produces response at distant sites and/or systemic response

- Can often elicit on parental history
This 18 mo boy presents with multiple pink-brown papules scattered randomly at trunk and extremities. Your history should focus on:

A) Family history of melanoma
B) Presence of localized symptoms (itching, swelling)
C) Gastrointestinal review of systems
D) Social history of arthropod exposure
E) B & C
“Urticaria Pigmentosa”
aka Maculopapular Cutaneous Mastocytosis

- Usually < 2 yo, not usually congenital
- Most common subtype
- Few to 100s of lesions
- Small “smudgy” pink-tan macules to papules
- Diff Dx: Nevi, CALMs, xanthomas, Langerhans cell histiocytosis
- Darier’s sign +
- Serum tryptase +/- elevated (usually mildly)
- Path: Mast cells w/o atypia in papillary dermis, often eos, +/- edema
- Symptoms more severe in 6-18 months after onset
- Spontaneous improvement, resolution in vast majority over years time
Maculopapular “UP”
Plaque Disease

Nodular Disease
UP + extracutaneous symptoms

• Not infrequent to have GI symptoms
• Nausea, abd pain/cramping, diarrhea
• GERD/food intolerance not allergy
• NOT indicative of systemic mastocytosis
• Treat with antihistamines, cromolyn
• When bx’d: ↑mast cells in GI Tract

• Less common to have respiratory, asthma-like symptoms
This newborn girl has diffusely leathery skin with bouts of blistering and erosions. Biopsy shows diffuse presence of mast cells. She should be monitored for:

A) Hypotension
B) Cutaneous malignancy
C) Respiratory infection
D) All of the above
Diffuse Cutaneous Mastocytosis

- Diffuse erythema, induration/infiltration
- +/- Associated alopecia
- Infancy, <3 yo
- Much rarer than UP
- Serum tryptase usually ↑ ↑ ↑ (in 100s)
- Does NOT usually progress to systemic involvement
- Slow improvement over time, to resemble more typical UP type

- Diff dx includes other blistering or infiltrative disorders, biopsy often necessary
- Can be life-threatening in early childhood – Shock, hypotension, anaphylaxis

Anesth Analg. 2008 August; 107(2).
Pediatric Cutaneous Mastocytosis...

Clonal proliferation, but most regress by or around puberty
Rare minority may go on to have adult-type systemic

Mastocytoma

Diffuse Cutaneous Mastocytosis

Urticaria Pigmentosa
Differentiate from Systemic...

- SM almost always presents in adulthood
- May have UP like lesions for years (often adult onset, not in childhood), then systemic manifestations
- 90% Indolent
- “Smoldering”
- Systemic + another non-mast cell hematologic proliferation
- Aggressive/leukemia

**Systemic Features:**
- Flushing/Pruritus
- Nausea/Vomiting
- Abd Pain/Diarrhea
- Vascular Instability
- Headache/”Brain Fog”
Systemic Mastocytosis

• Infiltrates usually seen in:
  – BM
  – Liver/Spleen
  – Lymph nodes
  – GI tract

• Workup:
  – Serum tryptase ↑ ↑ ↑ (total MC burden)
  – Bone marrow biopsy/aspiration
    • Confirmatory stains
    • Mutation analysis
Pediatric Cutaneous Mast Cell Disorders: Prognosis

• Various retrospective chart reviews:
  – 4-56% Complete resolution
  – 36-76% Partial improvement
  – 16-55% No change
  – 4-10% Worse over time
  – Most clinicians quote >50% chance of spontaneous resolution (by puberty?)

• 20 year small F/U study (Uzzaman et al, 2009)
  – 10/15 pts had complete resolution without treatment
  – Remaining 5 pts had major or partial regression
  – BM exam predictive of outcome: if +, persistent disease

• Ongoing study – Lawley et al.
Pediatric Cutaneous Mast Cell Disorders: Workup

- **Mastocytoma:**
  - Biopsy usually unnecessary if Darier’s sign +
  - No further w/u, unless ROS+

- **UP/Maculopapular & Diffuse Cutaneous Mastocytosis**
  - Similar to above, but
  - Clinical exam q 6-12 months
  - CBC/diff and **serum tryptase**, especially if extracutaneous findings/ROS:
    - <20 rules out systemic dz
    - 20-75 borderline
    - >75 nearly all have systemic sx (but not necessarily SM as a disease)
    - Follow annually if stable, or sooner if concerning sx/clinical changes
  - If abnormal labs and sx+, consider:
    - Repeat labs q 3-4 months to monitor
    - LFTs/Abd Ultrasound for HSM
    - BM biopsy for H&E, stains, mutation analysis
      - If +, more indicative of chronic/systemic dz
      - Does not seem to alter treatment
Treatment - Mastocytoma

• Avoid irritation
• Watchful waiting
• Mid- to high-potency topical glucocorticoids (+/- under occlusion) for symptoms
  • H1/H2 oral antihistamines
  • ? Local UV
  • Rarely, surgical excision
Treatment- UP/Maculopapular: Trigger Avoidance!

- Heat/Cold/Sunlight
- Exercise/Anxiety/Sleep Deprivation
- Pressure
- Venoms (Snake, Insect, Jellyfish)
- Alcohol (in med preparations)
- NSAIDs, Aspirin, Opioids/Dextromethorphan, Polymyxin B, Vancomycin, Ester Local Anesthetics
- Histamine-containing or releasing foods
  - Fermented (cheese, soy, vinegar, alcohol)
  - Many fruits/vegetables (eggplant, spinach, berries, strawberries etc)
  - Chocolate
- Radiocontrast Media (premedicate)
- ? Anesthetics
Treatment – UP/Maculopapular

- **For flushing/itching:**
  - (Scheduled) long acting H1 antihistamines
  - Antileukotrienes
  - ? Aspirin

- **For localized symptoms:**
  - Topical steroids
  - ? Topical cromolyn sodium 4% in hydrated petrolatum
  - ? PUVA

- **For GI symptoms:**
  - Cromolyn sodium oral solution
  - H2 antihistamines
  - Proton pump inhibitors
  - Antileukotrienes
Treatment – Diffuse/Bullous

- Similar to UP/maculopapular
- Strict trigger avoidance
- Scheduled antihistaminines

- Hospitalization/ICU during acute attacks
- Epinephrine prn
- ? Oral steroids
- ? Imatinib (if sensitive KIT mutation or in KIT816-unmutated patients with aggressive SM, but has been shown helpful in c-KIT-negative)
- ? PUVA

Role of imatinib in the treatment of pediatric onset indolent systemic mastocytosis: a case report.

Natural history and treatment of cutaneous and systemic mastocytosis.
Associations: Anaphylaxis

- ↑Tryptase associated with ↑risk severe anaphylactic rxns
- But in pts with only cutaneous signs (↑BSA/blistering) and low tryptase can demonstrate severe rxns
- Hymenoptera Venom Allergy (HVA) appears to be more common in masto pts
- Severe food allergy prevalence NOT increased
- +/- IgE Mediated (RAST testing)
- If adult develops severe/near-fatal anaphylaxis to bee sting, should be screened for mast cell disorder

Mastocytosis and Anaphylaxis
Immunology and Allergy Clinics of North America, 2017-02-01, Volume 37, Issue 1, Pages 153-164
Associations: Anaphylaxis

- Education/Awareness
- Probably more of a problem for known systemic disease
- Rx for Epi-Pen/Jr if appropriate
- Venom immunotherapy if known HVA + SM
- ER Protocols available
  - Epinephrine
  - Diphenhydramine
  - Methylprednisolone
  - Oxygen
  - Albuterol
Anaphylaxis – Anesthesia?

- Adult patients/SM—higher risk widespread MC degranulation in periop period
  - Case reports catastrophic CV collapse
- **NOT reported** in pediatric population
- Potential to cause unwarranted alarm in families

- Children with SM/elevated tryptase may warrant extra precautions, but this is a very limited group

- When able, anesthesia practitioners should:
  - Choose meds which cause minimal histamine release
  - Minimize anxiety as a potential trigger
  - Have periop prednisolone, antihistamines, epinephrine on hand
Back to mast cell physiology…

Blood Brain Barrier, Behavioral problems?

- Allergic/non-allergic triggers from the GI tract stimulate release of →
- Mast cell-derived vasoactive, inflammatory/neurotoxic mediators, increase gut-blood-brain-barrier permeability →
- Disruption BBB, stimulation brain mast cells to further release
- ? Molecules that increase BBB permeability and contribute to brain inflammation and ?autism

Schematic depiction of the proposed role of mast cell activation in brain inflammation and ASD.
Mastocytosis and Autism?

- Theoharides group thinks prevalence of ASD in mast cell disorders is 1/10.
- Compared to approx 1/100 in general population.
- Based on online questionnaire given to society members.
- NOT held up by current Peds Derm experience.
- Perhaps, slight increased prevalence of ADHD, but also seen in atopy, and in general population....

Theoharides and Zhang Journal of Neuroinflammation 2011

Exploring the prevalence of learning disabilities in children with cutaneous mastocytosis: A pilot cohort study. 
Seamens A1, Taussig B1, Penziner B1, Smidt A1, Lawley LP1. 

Mast cells in veterinary literature

- Most common skin tumor in dogs; 2\textsuperscript{nd} most common in cats
- Appear similar to human mastocytomas
- Dermal or subcutaneous
- Boxers, pugs, goldens, labs
- Grading of tumors in animals more important in determining prognosis
- Distant mets not uncommon, can be severe/fatal
Education & Awareness

- Trigger avoidance
- Alert bracelets
- Epi-Pen
- ? Protocols for procedures

- **Communication** with pediatrician, teachers, etc
- “Not contagious”

- The Mastocytosis Society
  www.tmsforacure.org

- www.mastokids.org