Pediatric Mastocytosis

- Accumulation of clonal mast cells
- Somatic activating KIT mutations
  - Codon 816 (35-40%, vs >80% in adults)
  - Other sites (35-40%)
  - None detectable (15-20%)
- Regression associated with codon 816 mutations
- No significant correlation found between mutation status and subtype or severity
- Rare familial mastocytosis with germline KIT mutations and autosomal dominant inheritance

Pediatric mastocytosis

- Unlike adults, mastocytosis in children is usually limited to the skin
- Rare involvement of the bone marrow, liver/spleen, other organs
- Revised cutaneous mastocytosis classification in 2016
  - Consensus from international group
- Interobserver concordance in subclassification of mac-pap only fair among mastocytosis experts, poor for general derms

Small, monomorphic “maculopapular” lesions

- Resembles conventional adult mastocytosis
  - Typical “urticaria pigmentosa”
  - <15% of pediatric patients
- Histology: spindle-shaped atypical mast cells (“sausages”)
  - CD25+ in bone marrow
- Tryptase more often elevated
- Later onset: ~60% >24 mos
- Longer duration: <5% <8 y, 60% ≥15 y, mean ~25 y

Large ± polymorphic “maculopapular” lesions

- “Well differentiated” mastocytosis
  - Variable sizes, some lesions ≥1 cm (includes “plaque”/“nodular” types)
- Occasionally familial
- Histology: round typical mast cells (“eggs”)
  - CD25-negative in bone marrow
- Tryptase rarely elevated
- Earlier onset: ~80% age ≤6 mos
- Shorter duration: ~70% <8 y, 95% <15 y; mean 6 y
  - Frequent fading/shrinking of lesions
Large/polymorphic "maculopapular" mastocytosis

- Fading/resolving over time
- Age 2 y, Age 7 y, Age 5 y, Age 4 y, Age 20 y
- Weichers et al. 2015
- Uzzaman et al. Ped Bl Cancer 2009

Diffuse cutaneous mastocytosis
- Generalized thickening of the skin without discrete lesions
  - Peau d'orange texture
  - May evolve to pseudoaxanthomatous
- Frequent blistering, flushing, GI symptoms due to mediator release
- Sometimes familial (KIT exon 8 or 9)
  - Persists, more often internal involvement
- Elevated tryptase levels, ↓ over time
- At birth or develops in early infancy
- Duration usually <8 y
- Matito et al. Immunol All Clin N Am 2018

Cutaneous mastocytomas
- Current definition: up to 3 lesions
- KIT mutations common
  - 1/3 codon 816, 1/3 other, 1/3 none
- Histo: entire dermis packed with mast cells
  - Be careful eliciting Darier sign in larger lesions
- Flushing can occur; rarely hypotension with large lesions
- Ma et al. Histopathol 2014

Blistering in mastocytosis
- Infants with large, thick lesions or diffuse involvement
  - Triggered by friction/irritation
  - Likely role of mast cell proteases
- Tendency usually remits by age 3 y

Mast cell mediators & mastocytosis symptoms
- Painful eruptions, headache, nausea, diarrhea, vomiting, anorexia, decreased appetite, irritability, sleep disturbance, failure to thrive, alopecia, lymphadenopathy, splenomegaly, hemorrhage
Symptoms in pediatric mastocytosis

- Systemic symptoms usually from skin MC mediator release
- Most common if diffuse or extensive skin involvement - Frequency correlates with # of skin lesions and skin symptoms
- Anaphylaxis very uncommon - 9/227 (4%) in recent series (vs 20-50% in adults)
- Neurodevelopmental disorder prevalence similar to general pediatric population

Pediatric mastocytosis: evaluation

- Serum tryptase level - Correlates with total mast cell burden and risk of severe symptoms - >20 ng/ml is minor criterion for systemic disease diagnosis - Measure (not during event) baseline and if elevated Q6-12 mos
- Assess for hepatosplenomegaly (clinical ± abdominal US) - In NIH study, of 53 children who had BM bx, all 19 with HSM had systemic disease, vs none of the 34 without HSM (all with ↑ tryptase &/or severe sx)
- KIT D816V mutation detection via PCR in peripheral blood - Negative in all 37 children with only cutaneous disease, positive in 21/28 (75%) of those with systemic disease
- Clinical diagnosis is routine for mastocytomas

Pediatric mastocytosis: possible triggers

- Emphasize to families: mastocytosis does not cause allergies, although may have more severe reactions
- Physical triggers: friction, heat, cold
- Alcohol, hot beverages, spicy foods, ? other foods/additives
- Mast cell degranulating medications - May include NSAIDs, aspirin, narcotics, dextromethorphan
- 2 peds series: 1.5% (2/133) of those who took NSAIDs had reaction
- Recent AAAAI report: NSAID avoidance not needed in all patients
- Some systemic anesthetics (local lidocaine injection OK)
- Vaccines: slightly higher risk of reaction, usually mild & no recurrence
- ? EpiPen® - If extensive disease/high mast cell burden or severe reactions

Pediatric mastocytosis: treatment

- Antihistamines for symptoms - Scheduled long-acting H1-antihistamine if frequent flares (± ↑ dose, multiple agents)
- H2-antihistamines for GI sx or as adjunct
- Oral cromelyn (low absorption) for GI sx
- Topical therapy - Cromolyn sodium 4% cream/lotion – www.mastokids.org/magic-masto-lotion - Class 1-3 corticosteroid in 2-6 week cycles ± occlusion; intralosomal TAC - Pimecrolimus cream - Hydrocolloid dressing for larger mastocytomas with frequent flares
- Oral azalide - May decrease mediator-related symptoms
- Oral/intravenous immunoglobulin (IVIG) - May decrease pruritus, activity, tryptase
- Kinase inhibitors (systemic dx) - midostaurin (codon 816, wt), imatinib (other mutations)
- Topical pimecrolimus for cutaneous mastocytosis - Can induce apoptosis of mast cells and prevent mediator production - 18 children, mean age 16 mos (3 mos-3.5 y), mastocytomas or mac-pap - Pimecrolimus BID x mean 8 mos (3-16 mos), 146 lesions tx - 27% disappeared, 67% faded; ~50% of raised lesions became macular

Baseline, age 21 mos
s/p pimecrolimus x 6 mos
Baseline, age 18 mos
s/p pimecrolimus x 12 mos
### Take home points on pediatric mastocytosis

- Mastocytomas are underrecognized and occasionally lead to systemic symptoms.
- Larger/polymorphic lesions → shorter duration.
- Hepatosplenomegaly and + KIT D816V in blood are markers of systemic disease.
- Treat symptomatically & avoid triggers — and unnecessary worry!

### Infantile sebopsoriasis / psoriasis

#### Childhood psoriasis

- Initial diaper/intertriginous rash with ‘double hit’, e.g. sebopsoriasis + candidal or bacterial (e.g. streptococcal) infection.
- This triggers a sudden, more widespread eruption of small pink, scaly psoriasiform papules.

### Perianal and vulvovaginal (perineal) streptococcal infection

- Favors children ages 2-7 y.
- Boys > girls for perianal.
- Sharply demarcated, bright red erythema.
- Pruritus, irritation, painful defecation/urination.
- Blood-streaked stools, vaginal discharge, fissures.
- Often also + GAS in throat.
- Can trigger guttate psoriasis.
- Tx: amoxicillin or 1st/2nd gen cephalosporin.
- Cefuroxime more effective than penicillin in one RTC.

### Streptococcal intertrigo

- Underrecognized cause of intertriginous eruptions in infants and toddlers.
- Sharply demarcated, intensely red.
- No satellite lesions.
- Foul odor.
- Fever and bacteremia can occur.
More Group A Strep

- Accounts for ≥20% of bacterial skin infections in patients with AD
  - Can mimic eczema herpeticum
- Patients more likely than those with S. aureus infections to:
  - Be febrile
  - Have facial/periorbital involvement
  - Be hospitalized

Psoriasis/psoriasiform eruptions triggered by TNF inhibitors

- Favors scalp (~50%), posterior auricular area, face, umbilicus
- Palmoplantar and flexural pustular eruptions
- ~10% of pediatric patients with IBD treated with TNF-inhibitor
  - Mean onset 10-20 mos (range, <1 mo - >5 y) after starting treatment
  - Therapy change in ~20%; ~half recur with another TNF-inhib
- Increased IL-17, 22 \rightarrow response to ustekinumab
- Also increased pimecrolimus/impetiginozation (~10%)

Eruptions triggered by TNF inhibitors in patients with IBD

Psoriasiform

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Systemic treatment of pediatric psoriasis

- Current FDA-approved biologic options
  - Etanercept (11/2016 for age ≥4 y)
    - PASI 75: ~55% at 12 weeks
  - Adalimumab (other indications age ≥2 y)
    - PASI 75: ~60% at 10 weeks
  - Ustekinumab (11/2017 for age ≥12 y; 8/2020 for age ≥6 y)
    - PASI 75: ~80-84% at 12 weeks (Q3 month dosing is helpful)
    - Ixekizumab (3/2020 for age ≥8 y)
    - PASI 75: ~80% at 12 weeks
  - Secukinumab (6/2021 for age ≥8 y)
  - PASI 75: ~80% at 12 weeks
  - Biologics vs methotrexate
    - PASI 75: Biologics (TNF-inhib) ~70% vs Methotrexate ~40% at 12+ weeks

CARD14-mediated pustular psoriasis (CAMPS) and CARD14-associated papulosquamous eruption (CAPE)

- Pustular psoriasis
  - Often generalized, childhood-onset ± plaque psoriasis
  - Palmoplantar pustulosis or PPK
- CAPE
  - Includes PRP (familial V), psoriasis variants
  - Onset usually in first year of life
  - PPK (80%), face/ear involvement
  - Follicular papules, islands of sparing
  - Dominant gain-of-function heterozygous CARD14 mutations
  - Increased IL-23 → Th17
  - Response to IL-12/23 inhibitors
  - CARD14 mutations

- Increased IL-23 → Th17
  - Response to IL-12/23 inhibitors
**Ustekinumab for CAPE**

**Pustular eruptions due to increased IL-1 or IL-36 signaling**

- **DIRA**: deficiency of the IL-1 receptor antagonist
  - Osteolysis, neonatal distress
  - Biallelic mutations/autosomal recessive
- **DITRA**: deficiency of the IL-36 receptor antagonist
  - Generalized pustular psoriasis, often childhood onset with systemic inflammation
  - Also ADEP, acrodermatitis of Hallopeau
  - Biallelic mutations—more severe disease
- **DIRA > DITRA**: response to IL-1 antagonist therapy (e.g. anakinra)
- **DITRA**: response to IL-17 inhibition

**Comorbidities in pediatric psoriasis: psoriatic march?**

- Increased prevalence of obesity
  - 30-50% in children/teens with mod-sev psoriasis, vs ~15% in general population
  - Often central adiposity, precedes diagnosis of psx in >90% of patients
- Increased insulin resistance and dyslipidemia
- Annual screening guidelines for pediatric psx patients
  - Blood pressure
  - BMI (body mass index)
  - Additional testing for DM, dyslipidemia, and fatty liver based on weight and other risk factors
  - Arthritis (~5-10%) screen (joint pain/stiffness/swelling, limp)
  - Screen for anxiety, depression, substance abuse