Diagnosing Mastocytosis: Cutting through the clutter

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Clinical manifestations and related mast cell mediators

<table>
<thead>
<tr>
<th>Skin</th>
<th>Histamine, PAF, PGD2, LTC4, LTD4, LTE4</th>
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</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>Histamine, PAF, LTC4</td>
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<tr>
<td>Rash</td>
<td>Histamine, PAF, LTC4</td>
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<tr>
<td>Blushing</td>
<td>Histamine, PAF, LTC4</td>
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<tr>
<td>Constipation</td>
<td>Histamine, PAF, LTC4</td>
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<tr>
<td>Fatigue</td>
<td>IL-6, TNF-α, IL-1β, IL-3, SCF, IL-6</td>
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<tr>
<td>Hypotension</td>
<td>Histamine, PAF, PGD2, LTC4, LTD4, LTE4</td>
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<td>Eosinophilia</td>
<td>SCF, IL-3, IL-β, chymase</td>
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<td>Inhibition of localized clotting</td>
<td>Histamine, PAF, LTC4</td>
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<td>Lymphadenopathy</td>
<td>IL-4, lymphokines</td>
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<td>Gastrointestinal</td>
<td>Histamine, PAF, LTC4</td>
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<td>Intestinal cramping</td>
<td>Histamine, LTC4</td>
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<td>Skeletal system</td>
<td>IL-4, IL-α, lymphokines</td>
</tr>
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<td>Bronchoconstriction</td>
<td>Histamine, PAF, LTC4</td>
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<td>Mucous and edema</td>
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PG, prostaglandin; PAF, platelet-activating factor; LT, leukotriene; SCF, stem-cell factor.

Supporting Evidence

- Clinical
  - Historical
    - Mast cell-mediator symptoms
    - Less atopic disease than general pediatric population
  - Cutaneous
    - Permanent pigmented lesions with a general distribution or diffuse thickening "peau d’orange" appearance
  - Other organ systems-mainly systemic disease

- Laboratory
  - Tryptase-represents overall mast cell burden
  - May trend down over time and elevates with mast cell activation
  - Urinary metabolites-correlates with serum tryptase
  - Hematologic-Usually WNL; may see ↑ lymphs, ↑ PT/PTT, ↑ PIs

- Sonographic
  - Hepatosplenomegaly with systemic disease, rare lymphadenopathy

Differential Diagnosis: Pediatrics

Most Likely
- Diffuse or localized hyper-pigmented macules
  - Café au lait spots
  - Neurofibromatosis
  - Albright syndrome
- Bullous Lesions
  - Chronic bullous disease of childhood
  - Linear IgA dermatosis
- Solitary or multiple nodules
  - Congenital nevus
  - Juvenile Xanthogranuloma

Consider
- No lesions
- Idiopathic flushing
- Diffuse or localized hyper-pigmented macules
- Post-inflammatory hyperpigmentation
- Secondary syphilis
- Chronic dermatitis
- Staphylococci infection
- Drug eruption
- Incontinentia pigmenti
- Bullous pemphigoid
- Solitary or multiple nodules

Always Rule Out
- No lesions
- Idiopathic anaphylaxis
- Diffuse or localized hyper-pigmented macules or papules
- Scabies
- Secondary Syphilis
- Addison's disease
- Lentigo
- Bullous Lesions
- Bullous impetigo of infancy
- Incontinentia pigmenti
- Solitary or multiple nodules
- Leukemia
- Lymphoma
Intestinal Biopsies-variability in measurement of urinary histamine
Bone Scans-nonspecific, nondiagnostic

Measuring the wrong mediator(s):

Serum Histamine Measurements:
- Simple faint; vasovagal episodes
- Panic attacks
- Spells-various types
- Disorders of hyper/hypo hidrosis
- Common flushing/climacteric flushing

Symptoms/signs that improve with medications not targeting mast cell mediators or their effects: Ex: medications for anxiety or depression

Food allergy
Non-anaphylactic reactions to bee stings, fire ants, horseflies

Common Laboratory Errors/Problems in Diagnosing SM
- Serum Histamine Measurements: samples must be processed rapidly
- Measuring the wrong mediator(s):
- Urinary 5-HIAA for diagnosing carcinoid
- Urinary Metanephrines for pheochromocytoma

A Word about Flushing
- Neurogenic-"Wet flushing"-sympathetic cholinergic neurons stimulate sweat glands
- Example: "Hot Flash"
- Dry flushing-direct vasodilation from vasoactive chemicals; no perspiration
- Example: Histamine, kinins, prostaglandins, nicotinic acid, amyl nitrite
- Most cases of "idiopathic" flushing

A Quick Tip for evaluating some patients suspected of having SM
- If no skin lesions of urticaria pigmentosa are present and serum tryptase is < 10 ng/mL, chance of SM is low; no bone marrow is needed
- If no skin lesions of urticaria pigmentosa are present and serum tryptase is > 10 ng/mL, check the urinary n-Methyl histamine or MIAA level
- If elevated, proceed with bone marrow biopsy. If normal, do not proceed with bone marrow biopsy.

What to look for
- Urticaria pigmentosa (UP) - most adults with UP have systemic mastocytosis
- Mediator symptoms, other suggestive clinical features (bee sting anaphylaxis, idiopathic anaphylaxis)
- Good response to MC mediator blockade
- Increased (baseline or symptom-associated) mast cell mediator levels:
  - Tryptase> 20 ng/mL;
  - Elevated 24 hour Urinary N-methyl histamine; 11β-PGF2α; LTE4
- Confirmation: bone marrow biopsy with specific findings
- Mast cell morphology (>=25%) show: spindle shape, hypo-granulated cytoplasm, oval decenteralized nucleus
- Mast cell phenotype: (+) CD 25
- C-kit Asp18Val mutation

Clinical symptoms/signs unlikely to be systemic mastocytosis or mast cell activation
- Hypertensive spells
- Symptoms that improve with medications not targeting mast cell mediators or their effects: Ex: medications for anxiety or depression
- Seizure activity; incontinence
- (Delayed) problems with memory
- Dementia
- Arthritic complaints involving small joints or involving muscles.
- Chronic hives; atopic dermatitis or eczema
- Delayed reactions to medications
- Rhinitis or rhinosinusitis
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- Spells-various types
- Disorders of hyper/hypo hidrosis
- Common flushing/climacteric flushing
- Panic attacks
- Spills-various types
- 1. Endocrine (Ex: pheochromocytoma, thyrotoxicosis, medullary thyroid carcinoma, insulinoma, hypoglycemia)
- 2. Cardiovascular (labile HTN, deconditioning, pulmonary edema, syncope, orthostatic hypotension, paroxysmal arrhythmias)
- 3. Psychologic (somatization disorder, hyperventilation)
- 4. Pharmacologic (withdrawal of adrenergic inhibitor, MAO treatment + tyramine, sympathomimetic ingestion, illegal drug ingestion, chlorpropamide-alcohol flush, vancomycin-red-man syndrome)
- 5. Neurologic (postural orthostatic tachycardia syndrome, autonomic neuropathy, migraine headache, seizure disorders, stroke, cerebrovascular insufficiency)
- 6. Anaphylaxis to bee stings
- 7. Recurring episodes of tachycardia not responding to cardiac medications (β-blockers) or a pacemaker
- 8. "Idiopathic" anaphylaxis
- 9. Males with osteoporosis
- 10. Eosinophilia
- 11. Anaphylactic response to NSAIDs (90-95% of mastocytosis patients do tolerate them)

Symptoms/signs with an increased likelihood of associated systemic mastocytosis
- Urticaria pigmentosa; positive Darier’s sign
- Mast cell mediator-related symptoms:
  - Flushing/warmth/pruritus/abdominal cramps/diarrhea/bronchospasm/tachycardia/ (pre)syncope
  - The symptoms respond to epinephrine administration & administration of medications targeting mast cell mediators such as antihistamines, sodium cromolyn
  - Anaphylaxis to bee stings
  - Recurring episodes of tachycardia not responding to cardiac medications (β-blockers) or a pacemaker
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  - Eosinophilia
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What are other common pitfalls when diagnosing mastocytosis?
- Carcinoid
  - Brief flush, worsened by epinephrine vs beneficial epinephrine response in SM
- Common flushing/climacteric flushing
- Spills-various types
  - 1. Endocrine (Ex: pheochromocytoma, thyrotoxicosis, medullary thyroid carcinoma, insulinoma, hypoglycemia)
  - 2. Cardiovascular (labile HTN, deconditioning, pulmonary edema, syncope, orthostatic hypotension, paroxysmal arrhythmias)
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- Simple faint, vasovagal episodes

Laboratory pitfalls in diagnosing SM and a Shortcut Decision Pathway for ordering a Bone Marrow Biopsy
- Hypertensive spells
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