***no patient handout*

Mastocytosis in adults - Skin

Contributors: Vanessa Holland MD, Jeffrey D. Bernhard MD, Belinda Tan MD, PhD, Noah Craft MD, PhD, Lindy P. Fox MD, Lowell A. Goldsmith MD, MPH, Michael D. Tharp MD

Synopsis

Mastocytosis is a term broadly referring to tissue mast cell hyperplasia. This proliferation is generally classified as either cutaneous, with or without systemic involvement, or systemic without cutaneous disease. Mastocytosis most commonly manifests as cutaneous disease (**urticaria pigmentosa**, **mastocytoma**), seen more often in children with involvement typically limited to the skin. In contrast, adult cutaneous variants frequently have systemic disease. See **telangiectasia macularis eruptiva perstans** (TMEP).

Systemic mastocytosis is a less common myeloproliferative variant comprised of a heterogeneous disease compilation. In general there is no age or sex predilection.The adult systemic condition has been further stratified numerous ways based on clinical criteria as well as on associated mutations, namely activating *c-kit* mutations. This discussion is based on the most recent 2008 World Health Organization (WHO) classification. WHO classified four major subtypes of extracutaneous systemic mastocytosis: (1) indolent systemic mastocytosis, (2) systemic mastocytosis with associated clonal hematologic non-mast cell lineage disease (SM-AHNMD), (3) aggressive systemic mastocytosis, and (4) **mast cell leukemia**.

1. Indolent systemic mastocytosis is most frequently seen. Mast cells primarily, yet modestly, infiltrate the bone marrow and may involve other organs, including the spleen, liver, and gastrointestinal tract. Because the disease is typically limited in children and often chronic and stable in adults, prognosis is favorable.

2. Systemic mastocytosis with a chronic myeloproliferative neoplasia (SM-AHNMD) has a course and prognosis determined by efficacy of management of the underlying disease.

3. Aggressive systemic mastocytosis, in which there is organ destruction from a mast cell infiltrate, is rare and should promote investigation for mast cell leukemia or other hematologic disorders such as myelodysplastic syndromes, myeloproliferative or myelodysplastic disorders, acute myeloid leukemia, and chronic myeloproliferative neoplasia.

4. Mast cell leukemia is seen in two-thirds of patients with aggressive systemic mastocytosis and portends rapid progression that could potentially result in multi-organ failure. It is defined as greater than or equal to 20% mast cells in bone marrow smears and by circulating mast cells, often greater than or equal to 10% in peripheral smears. Pancytopenia can occur and may explain instances in which peripheral mast cells comprise less than 10% of the differential.

Codes

ICD10CM:
Q82.2 – Mastocytosis

SNOMEDCT:
397016004 – Systemic Mast Cell Disease

Look For

Symptomatology is related to mast cell mediator release, ie, histamine, cytokines, eicosanoids. GI complaints most commonly accompany or herald disease, including nausea, vomiting, and diarrhea. Other symptoms include pruritus, flushing, blushing, malaise, tachycardia, headaches, cognitive disorganization, weight loss, and respiratory difficulty. As the majority of cutaneous mast cell-mediated diseases are asymptomatic, the presence of such should warrant investigation into potential systemic involvement. Organomegaly is often absent; however, it can manifest with hepato- and splenomegaly when it does occur.

Systemic mastocytosis is an extracutaneous classification and thus lacks cutaneous lesions beyond the apparent symptomatic evidence.

With regard to cutaneous disease, cutaneous mastocytosis in adults tends to be distinct from those related conditions seen in children, ie, urticaria pigmentosa and diffuse mastocytomas. The most common adult variant manifests with small (less than 1 cm) pink to reddish-brown macules and papules with fine telangiectasias and hyperpigmentation upon close inspection. Lesions are most abundant on the trunk and proximal extremities. Such lesions may spontaneously resolve but often reappear. Darier sign is a classic marker of cutaneous mastocytosis: upon stroking a lesion, it urticates; ie, it becomes erythematous and edematous and looks like a hive.

TMEP is an even less common variant composed of lesions with a telangiectatic predominance and minimal hyperpigmentation. Cutaneous lesions tend to be chronic and stable in TMEP, and it is generally thought to be benign, as systemic involvement is seen far less commonly in TMEP relative to other adult cutaneous mastocytoses. Darier sign can be especially helpful in making the diagnosis.

Mastocytomas composed of larger individual or diffuse pink plaques have been reported but are thought to be exceedingly rare in adults. Likewise, urticaria pigmentosa, typically presenting with numerous reddish-brown urticating macules, is seen predominantly in infants and children although it may be seen in adults.

Cutaneous mastocytotic lesions tend to manifest more as dusky, violaceous, and hyperpigmented in darker skin (as opposed to being pinker, with less hyperpigmentation, in lighter skin).

For further discussion of these conditions, see Urticaria Pigmentosa, Mastocytoma, and TMEP in VisualDx.

Diagnostic Pearls

Systemic symptoms are key. Multiple episodes of anaphylaxis (eg, related to drugs) should lead to a consideration of mastocytosis. Any cutaneous variant or suspicion of systemic disease should warrant a thorough review of systems.

Differential Diagnosis & Pitfalls

- Mast cell activation syndrome – The more recently termed mast cell activation syndrome (MCAS) describes patients who have multiple mast cell mediator-induced symptoms that do not meet the WHO criteria (see Best Tests) for diagnosis of systemic mastocytosis when other underlying diseases have been excluded.

- **Pheochromocytoma** – Patients with an underlying pheochromocytoma present with paroxysms of hypertension, tachycardia, and diaphoresis. Pallor is often seen during these paroxysms, with flushing following resolution of the attack.

- **Carcinoid syndrome** – Patients with foregut carcinoid tumors may suffer from carcinoid syndrome, which classically manifests with gastrointestinal complaints. Chronic watery diarrhea with associated weight loss is the most frequent complaint; however, patients may also complain of abdominal pain, constipation, and nausea. A persistent and intense salmon-pink to red flushing occurs in these patients. As opposed to foregut carcinoid tumors, patients with midgut tumors typically demonstrate a more cyanotic flushing. Due to an acquired niacin deficiency, pellagra-like cutaneous symptoms are also seen.

- **Essential telangiectasia**

Best Tests

Serum total tryptase greater than 20 ng/mL is suggestive of systemic disease and thus warrants referral to hematology-oncology for additional work-up.

With regard to systemic involvement, the bone marrow involvement is often infiltrated, and thus bone marrow biopsy is warranted. Mast cell, eosinophil, lymphocyte (MEL) lesions describe a mixed inflammatory infiltrate associated with the mast aggregates and thus distinguish mastocytic bone marrow involvement. Skeletal lesions also commonly occur in adult mastocytosis, as opposed to mastocytoses in the pediatric population. Radiographically, these lesions may appear as either radio-opacities or radiolucencies, with the axial bones most frequently involved, ie, spine, pelvis, and skull. Demineralization progressing to osteoporosis and osteosclerosis may occur in patients with diffuse skeletal involvement. While splenic and hepatic infiltration may also occur with splenomegaly and/or hepatomegaly, lymph node involvement is less common and indicative of more advanced disease. A mixed organic brain syndrome is also described, manifesting with fatigue, irritability, memory loss, and interpersonal and motivational deficits.

The WHO major criterion to define systemic mastocytosis is multifocal dense infiltrates of abnormal mast cells (greater than 15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s).

The WHO minor criteria include:

1. Mast cells in bone marrow or in histologies of other extracutaneous organ(s) showing an abnormal morphology (greater than 25%)
2. Mast cells in bone marrow expressing CD2 and/or CD25
3. *c-kit* mutation in tyrosine kinase in mast cells in extracutaneous organ(s)
4. Serum total tryptase greater than 20 ng/mL

With regard to cutaneous disease, skin biopsy elucidates the mast cell proliferation. The mast cell infiltrate is predominately in the upper third of the dermis and, depending on the variant, may be described as sparse (as in urticaria pigmentosa and TMEP) to dense (as in a cutaneous mastocytoma). Darier sign is classic marker of cutaneous lesions in which the lesion urticates, becoming erythematous and edematous, upon stroking by the clinician.

Histopathology Findings:
Common features

- Perivascular or diffuse aggregates of mast cells involving the upper dermis
- Polygonal or spindle-shaped cells with abundant, granulated, amphophilic cytoplasm

Occasional features

- Hyperpigmentation of the basal layer of the epidermis
- Papillary dermal edema
- Subepidermal vesiculation
- Telangiectasia in the superficial dermis
- Stromal fibrosis
- Eosinophils
- Extension of the infiltrate into the deep dermis or subcutis

Management Pearls

A mast cell trigger avoidance list should be provided. Such triggers include alcohol, aspirin, NSAIDs, narcotics (morphine, codeine, etc), heat, friction, polymyxin B sulfate, and systemic anesthetics (lidocaine, d-tubocurarine, metocurine, succinylcholine, thiopental, etomidate,

enflurane, and isoflurane).

Safe systemic anesthetic alternatives include propofol, fentanyl, and vecuronium bromide.

An epinephrine pen should be provided for intramuscular injection as needed for anaphylaxis.

Therapy

Antihistamines should be initiated with a non-sedating antihistamine every 24 hours.

Non-sedating antihistamine examples include over-the-counter:

- Cetirizine 10 mg, or
- Fexofenadine 180 mg, or
- Loratadine 10 mg.

These may be given individually every 12 hours or every 24 hours, or in combination, split once in the morning and once at bedtime, as dependent on symptomatology.

Sedating antihistamines may be given every 24 hours at bedtime in combination with a morning non-sedating antihistamine or as rescue antihistamines:

- Diphenhydramine 25 mg – Instruct patients: 25-50 mg every 24 hours at bedtime as needed in combination with a non-sedating morning antihistamine. Alternatively, 25 mg every 6 hours as needed for rescue dosing. Note: Caution in elderly patients, or
- Hydroxyzine 10-25 mg – Instruct patients: 10-50 mg every night at bedtime as needed in combination with a non-sedating morning antihistamine. Alternatively, 10-25 mg every 6 hours as needed for rescue dosing. Note: Caution in elderly patients.

H2 antagonists may added if the above fails, eg, ranitidine 150 mg every 12 hours.

Epinephrine – EpiPen 0.3 mg IM once as needed for anaphylaxis.