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Case Presentation

The Illinois Society of Allergy, Asthma, and Immunology
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A 64 year old male with no significant past medical history presents to his primary care physician with night sweats for 1 year

Initial visit to PCP: 8 months ago

- Reported drenching night sweats ongoing for 1 year
- No fevers, unintentional weight loss, enlarged lymph nodes, abdominal pain, diarrhea, joint pain, or other symptoms
- Routine cancer screenings up to date
- Physical exam notable for faint petechial rash over the dorsum of the bilateral feet

Night sweats: differential diagnoses

- Malignancy
- Infection
  - Tuberculosis
  - HIV
  - Bacteremia
  - Endemic infections
- Endocrine
  - Hyperthyroidism
  - Pheochromocytoma
  - Carcinoid syndrome
  - Alteration in estrogen/androgen levels
  - Insulinoma
  - Acromegaly
- Medications
  - Cholinergic agonists/cholinesterase inhibitors
  - Hypoglycemic agents
  - Antidepressants
- Neurologic
  - Autonomic dysreflexia (e.g. history of spinal cord injury)

Petechial rash: differential diagnosis

- Hematologic
  - Thrombocytopenia, coagulation defects
    - Sepsis
    - Idiopathic thrombocytopenic purpura (ITP)
    - Thrombotic thrombocytopenic purpura (TTP)
    - Hemophilia
    - Disseminated intravascular coagulation
- Malignancy
  - Leukemia
  - Lymphoma
- Infectious
  - Meningococcemia
  - Disseminated gonococcal infection
  - Rocky Mountain Spotted Fever
  - Endocarditis
- Rheumatologic
  - Vasculitis
    - Lupus
    - EGPA
    - IgA vasculitis
- Medications
  - Bactrim, carbamazepine, valproic acid (from decreased platelets)
- Trauma

Workup: 8 months ago

- CBC with differential: normal
- CMP: normal
- ESR: normal
- CRP: normal
- TSH: normal
- Urinalysis: normal
- ANA: 1:160 speckled
- C-ANCA, P-ANCA: normal
- Autoimmune disease panel: normal
- Quantiferon: normal
- Hepatitis C Ab: normal
- HIV: normal
- Blood culture: normal
- PT/INR: normal
- PSA: normal
- **Tryptase 14.6 mcg/L**
- Chest X-ray: normal

PCP follow-up visit: 1 month ago

- Night sweats have worsened – now having nightly drenching sweats
- Rash persists and now mainly shows up after showers
- Review of systems otherwise negative
- Physical exam notable for faint petechial rash on bilateral dorsum of feet
- PCP orders more labs and imaging (next slides)

Workup: 1 month ago

- CBC with differential: normal
- CMP: normal
- TSH: normal
- Urinalysis: normal
- Quantiferon: normal
- Blood culture: normal
- Urine culture: normal
- IgM, IgG, IgA levels: normal

- **Free kappa light chain 2.48 mg/dL [0.33-1.94]**
- Free lambda light chain 0.72
- **Free K/L light chain ratio 3.44 [0.26-1.65]**
- SPEP and UPEP: normal

Tryptase: 41.7 mcg/L

Imaging

CT Abdomen and Pelvis

- **No definite explanation for the patient's night sweats is identified on this exam.**
- A few small pulmonary nodules are indeterminate. If this patient is at high-risk for primary lung malignancy, a follow-up chest CT can be considered in 12 months.
- There is a 0.9 cm lesion arising from the upper pole of the right kidney that measures higher than simple fluid density. It is unchanged in size since 1/30/2016 and previously measured closer to simple fluid density. This is favored to represent a hemorrhagic/proteinaceous cyst, but follow-up renal ultrasound in 1 year is recommended.
- Postsurgical changes within the sigmoid colon. No evidence of bowel obstruction or acute diverticulitis.

Referrals

- Allergy/Immunology for elevated tryptase
- Hematology/Oncology for evaluation of plasma cell dyscrasias

History of Present Illness: A/I Clinic

- Drenching night sweats ongoing for 1 year, occurring almost nightly for the past 6 months
- New rash over the past couple of years – flat, brown spots that have been spreading, now present all over his body. No itchiness or burning.
- In the past year, he also noticed flat, red spots over his skin that show up for 15 minutes, typically in the morning after a shower. Rash triggers include showers and hot weather. No itchiness or burning. Started taking Zyrtec 5mg that reduced occurrence of symptoms.
- Chronic cough for 20 years – dry cough in the morning that clears up over the course of the day, associated with post-nasal drip. Improved with Azelastine nasal spray. No improvement with albuterol or omeprazole.

Past Medical History

Allergy history:

- Food allergy: none
- Bee sting reaction: none
- Eczema: none
- Asthma: none
- Adverse reaction to NSAIDs: none
- Anaphylaxis: never
- Medication allergy: rash over chest after taking an oral penicillin many years ago that resolved overnight without treatment (details unclear)

Medical/Surgical history:

- Diverticulosis s/p colectomy 5 years ago

Family history: Grandmother – breast cancer at a young age

Social history:

- Runs a business, no specific occupational exposures
- Alcohol: occasional glass of wine
- Never smoker
- No pets

Current medications:

- Azelastine nasal spray 2spn BID
- Zyrtec 5mg QD PRN

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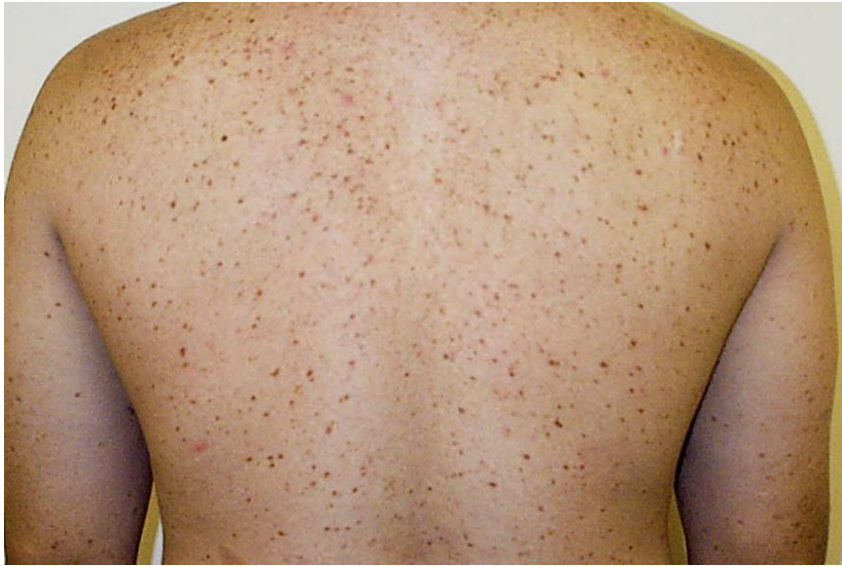
Review of Systems

- General: **+ night sweats**; no fevers, chills, weight loss, fatigue, flushing
- HEENT: **+ post-nasal drip**
- Cardiovascular: no chest pain, edema
- Pulmonary: **+ chronic cough**; no shortness of breath, wheezing
- Gastrointestinal: **+ diarrhea once every few weeks**; no abdominal pain, nausea, heartburn
- Hematological: no easy bruising
- Skin: **+ rash**, no dermatographism
- Neurologic: **+ some memory difficulties over the past 2 years**; no concentration difficulties, no syncope
- Musculoskeletal: **+ cramping in the legs and feet nightly**
- Immunological: no history of frequent infections

Physical Exam

BP 124/75 | Pulse 68 | Temp 98 °F (36.7 °C) | SpO2 98%

- Gen: Well-appearing gentleman in no acute distress
- Head: NCAT
- Eyes: Conjunctiva non-injected. Sclera anicteric.
- Ears: Tympanic membranes pearly grey, light reflex intact.
- Nose: No obstruction, bleeding, purulent drainage
- Mouth/Throat: OP clear, no erythema or exudates
- Neck: No lymphadenopathy
- CV: RRR, s1 and s2 heard, no murmurs, rubs, gallops
- Lungs: CTAB, no wheezes or crackles
- Abd: Soft, non-tender, non distended, no hepatosplenomegaly
- Ext: No lower extremity edema. No cyanosis or clubbing.
- **Skin: Diffuse macular reddish brown hyperpigmented lesions; development of erythema and urticaria upon stroking of an individual lesion**



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Differential diagnosis

Causes of Chronically Elevated Serum Tryptase

- Mast cell disease
  - Systemic mastocytosis (SM)
  - Cutaneous mastocytosis (CM)
  - Mast cell activation syndrome (MCAS)
- Familial hypertryptasemia (FHT) with or without mast cell activation
- Hematologic disorders
  - 1/5 of myelodysplastic syndromes, myeloproliferative disorders, myeloid neoplasms
  - Acute myeloid leukemia
  - Mast cell leukemia
  - Mast cell sarcoma
  - Hypereosinophilia with myeloproliferative features
- Cardiovascular disease (coronary artery disease)
- End stage renal disease
- Onchocerciasis (river blindness) under therapy (Ivermectin)
- False positive elevation – rheumatoid factor, heterophile antibodies

Lee. Int Arch Allergy Immunol 2020;181:357–364

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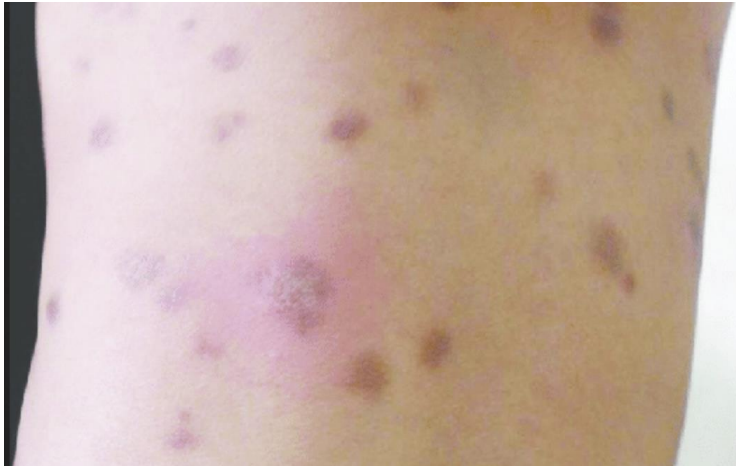
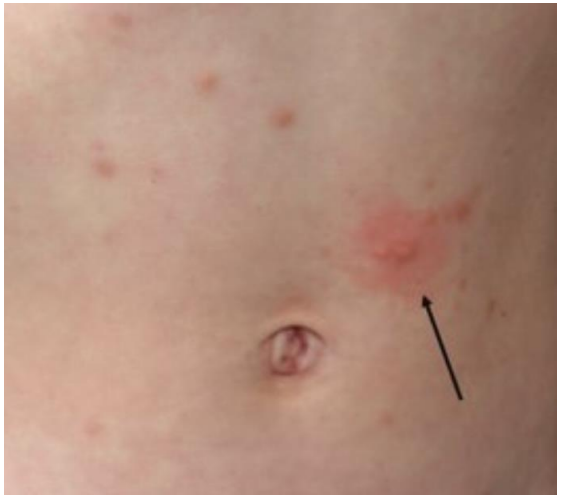
Patient's rash

- Our patient's rash was consistent with **urticaria pigmentosa**
- **Darier's sign**
  - Stroking a lesion 5 times using moderate pressure with a tongue spatula leads to erythema or urticaria over or around the lesion within approximately 5 minutes
  - Suggestive of the presence of mast cells within the lesion
  - Highly specific diagnostic feature of cutaneous mastocytosis
  - Antihistamines may blunt response





Working diagnosis

- Cutaneous mastocytosis
  - Classic skin lesions – multiple, monomorphic, reddish brown macules
    - Maculopapular cutaneous mastocytosis, aka urticaria pigmentosa (MPCM/UP)
    - Positive Darier's sign
    - Exacerbated by triggers known to cause mast cell degranulation in patients (e.g. hot baths)

Condition we need to rule out

- Systemic mastocytosis (SM)
  - Most adults with MPCM/UP will prove to have systemic disease
    - Patient had symptoms of mast cell mediator release
      - Night sweats more unusual
      - Fatigue, diarrhea, musculoskeletal pain, “brain fog”
  - Among adults with SM, approximately 80 percent have MPCM/UP
    - “Mastocytosis in the skin” (MIS) = presence of skin findings in patients who have not yet been evaluated to determine whether they have systemic disease

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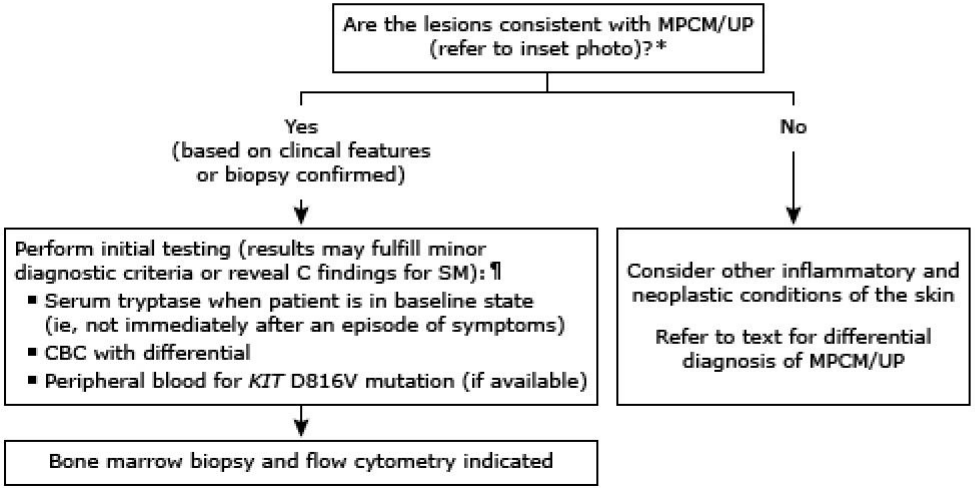
Further workup?

Decision to perform bone marrow biopsy in an adult with suspected systemic mastocytosis (SM) presenting WITH skin lesions



Completed:
- Tryptase
- CBC with differential

Still need:
- Peripheral blood *KIT* D816V mutation
- BM biopsy and flow cytometry

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KIT D816V mutation

- Most common *KIT* mutation
  - Adenine-to-thymine (A>T) base substitution
  - Amino acid changed from **aspartic acid (code letter D)** to **valine (code letter V)** at amino acid **816**
- *KIT* gene codes the receptor for stem cell factor which is needed for mast cell survival
- Mutation leads to constitutive activation of the receptor tyrosine kinase, impaired apoptosis, increased mast cell maturation
- Present in most patients with SM (and in some CM patients)
- In children with CM, the D816V mutation has been found in skin lesions in at least 20 percent
- Can be performed on bone marrow or peripheral blood

Bone marrow biopsy: what to look for

- Histochemistry
  - Mast cells identified by staining with antibodies to tryptase and/or KIT (CD117)
  - Stains to detect CD25 (IL-2 receptor alpha chain) and CD2 (LFA-2)
    - Expressed in SM but not in normal or reactive mast cells
- Flow cytometry
  - Mast cells expressed as $CD117^{high}$ immunoglobulin E $(IgE)^{positive}$ population
  - Expression of CD2 and CD25
  - Double-positive cells expressing both KIT (CD117) and CD25 are considered aberrant mast cells
- D816V *KIT* mutational analysis

Our patient: results

Immunohistochemistry

CD3	Highlights scattered small T cells
CD20	Highlights scattered small B cells; no atypical aggregates identified
CD2	Positive in the T cells; appears negative or weak in the mast cells
CD25	Strongly positive in the mast cells
Tryptase	Highlights dense clusters of mast cells in nodules and interstitially throughout the marrow; frequent spindle-shaped mast cells are noted
CD 117	Similar findings to tryptase (~5-10% of cellularity)
CD138	~3% plasma cells scattered and in small clusters

- Peripheral blood: positive for D816V *KIT* mutation
- Bone marrow results:
  - Positive for D816V *KIT* mutation
  - Path report: The morphologic and immunophenotypic findings (including multiple nodules with dense aggregates of >15 mast cells, atypical spindled mast cell morphology, and aberrant CD25 expression on the mast cells) in conjunction with the previously reported elevated tryptase and positive c-KIT D816V mutation are compatible with systemic mastocytosis. No morphologic or immunophenotypic evidence of a plasma cell neoplasm

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Diagnosed with: systemic mastocytosis

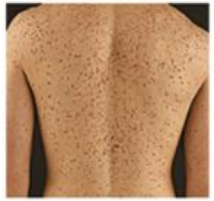
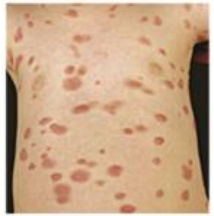
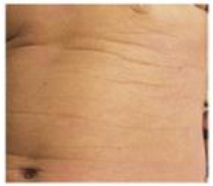
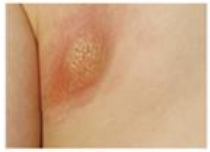
Mastocytosis: Epidemiology

- Estimated prevalence (all forms) 1/10,000
- Most adults have systemic disease
  - Cutaneous forms <5% in adults
  - Among adults with systemic mastocytosis, approximately 80 percent have MPCM/UP
- Most children (>90%) have disease limited to the skin, which improves/resolves during puberty

Brokchow et al. Immunol Allergy Clin North Am. 2014;34(2):283

Cutaneous mastocytosis

- Excessive mast cells in the skin
- Do not fulfill diagnostic criteria for systemic mastocytosis
- No evidence of organ involvement except skin

Subforms	Variants	Typical manifestations
Maculopapular cutaneous mastocytosis (syn. urticaria pigmentosa)	Monomorphic	
	Polymorphic	
Diffuse cutaneous mastocytosis		
Cutaneous mastocytoma		

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Hartmann et al. J Allergy Clin Immunol. 2016 Jan;137(1):35-45

Poll

- Which of the following is not a minor criterion for the diagnosis of systemic mastocytosis?

A) Persistent serum tryptase elevation >20ng/mL

B) *KIT* D816V mutation in the bone marrow or blood

C) Biopsy (bone marrow or extracutaneous) showing > 25% mast cells with spindle-shaped or atypical morphology

D) Episodic signs and symptoms of systemic mast cell mediator release

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Systemic mastocytosis: diagnosis

Major criterion
≥15 mast cells in aggregates detected in sections of BM and/or other extracutaneous organs
Minor criteria
1. In biopsy (BM or extracutaneous), ≥25% of mast cells in the infiltrate are spindle shaped or have atypical morphology, or >25% of mast cells in the BM aspirate smears are immature or atypical 2. Activating point mutation at codon 816 of *KIT* in BM, blood, or another extracutaneous organ 3. Mast cells in BM, blood, or extracutaneous organ express CD25 +/- CD2 (in addition to normal mast cell markers) 4. Serum tryptase persistently >20 ng/mL (unless there is an associated myeloid neoplasm)

Major criterion + 1 minor criterion

OR 3 minor criterion

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Systemic mastocytosis: signs and symptoms

- Skin findings
- Symptoms from mediator release
  - Episodic signs/symptoms of mast cell activation affecting at least 2 organ systems (flushing, tachycardia, diarrhea, fatigue, musculoskeletal pain)
- Noncutaneous organ infiltration (e.g. liver, spleen)
- Advanced forms -> cytopenias due to bone marrow infiltration, portal hypertension and ascites from liver infiltration, nonimmune hemolytic anemia from hypersplenism

Systemic mastocytosis: subtypes (WHO)

- Indolent systemic mastocytosis (ISM)
- Smoldering systemic mastocytosis (SSM)

Advanced

- Aggressive systemic mastocytosis (ASM)
- Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN)
- Mast cell leukemia (MCL)

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"B" findings:	"C" findings:	Features of MCL:
1. Bone marrow biopsy showing >30% infiltration by mast cells (focal, dense aggregates) and/or serum total tryptase level >200 mg/mL. 2. Signs of dysplasia or myeloproliferation in nonmast cell lineage(s) but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (SM-AHN) with normal or only slightly abnormal blood counts. 3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.	1. Bone marrow dysfunction manifested by one or more cytopenia (ANC <1 × 10^9/L, Hb <10 g/dL, or platelets <100 × 10^9/L) but no obvious nonmast cell hematopoietic malignancy. 2. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension. 3. Skeletal involvement with large osteolytic lesions and/or pathologic fractures. 4. Palpable splenomegaly with hypersplenism. 5. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates.	Bone marrow biopsy shows a diffuse infiltration, usually compact, by atypical, immature mast cells. Bone marrow aspirate smears show ≥20% mast cells.

- "B" findings indicate high mast cell burden and involvement of multiple hematopoietic lineages but no organ damage
- "C" findings indicate organ damage by mast cell infiltration

Indolent and smoldering systemic mastocytosis
Indolent systemic mastocytosis (ISM) ▪ SM diagnostic criteria; no "C" findings
Smoldering systemic mastocytosis (SSM) ▪ SM diagnostic criteria plus two or more "B" findings; no "C" findings
Advanced systemic mastocytosis
Aggressive systemic mastocytosis (ASM) ▪ SM diagnostic criteria plus "C" findings; no features of mast cell leukemia
Mast cell leukemia (MCL) ▪ SM diagnostic criteria plus features of MCL
Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) ▪ SM diagnostic criteria plus clonal hematologic nonmast cell lineage disorder (eg, MDS, MPN, AML, lymphoma, other)

Cutaneous	Prognosis
Urticaria pigmentosa	Polymorphic – usually resolves by puberty Monomorphic – more persistent, tendency to progress to SM
Diffuse cutaneous mastocytosis	Increased risk of SM
Mastocytoma	Usually resolve spontaneously after several years

Systemic	Prognosis
Indolent systemic mastocytosis	Generally low morbidity, normal life expectancy <3% patients progress to a more severe form
Smoldering systemic mastocytosis	Inferior survival and higher risk of progression to more severe disease compared to ISM
Aggressive systemic mastocytosis	Poor prognosis
Systemic mastocytosis with an associated hematologic neoplasm	Prognosis mainly depends on associated hematologic neoplasm
Mast cell leukemia	Poor prognosis

Systemic mastocytosis: Management

- Indolent and smoldering systemic mastocytosis
  - Epi Pen twin pack at all times (anaphylaxis more common than advanced forms)
  - Avoidance of triggers (heat, stress, etc.)
  - Symptoms of mast cell mediator release
    - Antihistamines
    - Mast cell stabilizers
  - Screening for osteoporosis
- Advanced forms
  - Midostaurin (*KIT* inhibitor) suggested as initial treatment of most patients – all subtypes respond
  - Variable – Avapritinib, Cladribine, other tyrosine kinase inhibitors, interferon; many other agents are under investigation (Ripretinib, Brentuximab vedotin etc)
  - Allogeneic HCT may be an option who failed initial therapy or relapsed

Our patient

- Diagnosed with indolent systemic mastocytosis (no “C” findings) and undergoing supportive management. Currently on Zyrtec 10mg daily.
- Following with hematology/oncology
  - Underwent abdominal fat pad FNA biopsy to rule out amyloidosis
  - MRI of pelvis, cervical, thoracic, lumbar spine performed with no focal myelomatous lesions identified
  - Pending DEXA scan

Take home points

- Most adults who present with MPCM/UP have systemic mastocytosis; workup is warranted
- Darier's sign is highly specific for cutaneous mastocytosis
- Review the diagnostic criteria for systemic mastocytosis and its subtypes
- Patients with systemic mastocytosis should be educated on the increased risk of anaphylaxis. Anaphylaxis is more common in ISM and SSM compared with advanced forms of the disease.

Thank You

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