Mystery Case

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Objectives

- Clinical Presentation
- Differential Diagnosis
- Diagnosis
- Management

HPI

- 46 yo F presents to hospital with chief complaint of “hives”
  - Was in her normal state of health until 4 days prior to admission when she developed a sore throat, generalized aches, chest pressure and an isolated hive behind her right ear
    - History of chronic idiopathic urticaria was given to her by another allergist in Tennessee
  - The following morning, she awoke with widespread hives
  - Was seen in ED where a CXR and EKG were done but were benign
  - Treated with solumedrol, famotidine, diphenhydramine, albuterol nebs
  - Was discharged home with plan to follow up with her PCP

HPI (continued)

- The following day, her symptoms worsened so she returned to the ED
  - At this time, she complained of facial swelling, lower lip swelling, and difficulty swallowing
  - She was ultimately discharged without additional intervention and told to follow up with her PCP
  - The following morning, she contacted her PCP because her lip swelling continued to worsen, and her PCP recommended direct admission to the hospital for further work up and management

HPI (continued)

- She has not had new recent exposures or travel
- She has no oral or vaginal ulcerations
- Additional history from patient and husband reveal past episodes of generalized hives that resolve without residual marks on her skin
  - Episodes started approximately seven years ago when she was living out of state
  - Episodes of hives vary in duration and frequency
  - She reports not having episodes for “years at a time” and then having episodes several times in two month period that can last days at a time
  - Reports being hospitalized for fluids with at least two episodes as the diarrhea is so severe
  - She also recently completed a 7 day course of clindamycin for a tooth abscess

History

PMH

- GERD
- Asthma
- Fibromyalgia
- Heart murmur
- HTN
- HA

PSH

- Tubal ligation
- Hysterectomy
- Hemithyroidectomy

History (continued)

Family History

- Mental illness
- HTN
- CAD

Social History

- Tobacco 5-10/day since she was 12 yrs old
- Denies EtOH or IVDA
- Lives with husband; has 3 adult children
- No pets
- Currently on disability for the past 5yrs because of mental illness and fibromyalgia
- No recent travel

Allergies

GI Bleeding, Hives/Urticaria, Swelling/Edema

- ASA
- Ibuprofen

Anaphylaxis

- Latex
- Bee stings
- PCN

Current Home Medications

- Gabapentin 300 mg by mouth every 6 hours.
- Cetirizine 10 mg by mouth daily.
- Hydroxyzine 50 mg by mouth 3 times a day.
- Tramadol 50 mg by mouth 3 times a day as needed.
- Topiramate 50 mg by mouth 2 times a day.
- Verapamil 240 mg by mouth daily.
- Pantoprazole 40 mg by mouth daily
- Cyclobenzaprine 5 mg by mouth daily as needed.
- Benadryl 25 mg by mouth every 4 hours as needed itching.
- Pepcid 20 mg by mouth daily.

Review of Systems

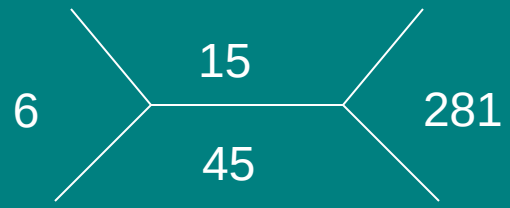
- All other systems have been reviewed and are negative except:
  - **Gen:** Dizzyness, Lightheadness
  - **ENT**: Throat Pain, Itchy tongue, Swollen lips
  - **Respiratory**: Shortness of breath
  - **Cardiac**: Chest Pain, Dyspnea on exertion.
  - **Gastrointestinal**: Severe Nausea, Diarrhea
  - **Skin**: Pruritis, Rash, Hives, Flushing.

Physical Examination

- Vital Signs
  - T 36.1; P 74; R 18; BP 129/81;SpO2 100%

- All organs were within normal limits except the following:
  - Skin:
    - **Face**: swollen, diffusely erythematous
    - **Arms, thighs, chest**: polycyclic, annular patches with erythematous borders, lacey with central clearing through out no scale
    - **Back**: diffusely erythematous, no discrete lesions
    - **Abdomen**: clear
    - **Lower legs, feet**: clear

Labs



No differential ordered

Ca^{2+}: 8.1

Protein 5.5 (L)
Albumin 2.5 (L)
Bili Total 0.3
Alk Phos 61
ALT 21
AST 16

CRP: <0.3
ESR: 9

Protime: 10.8

PT, INR: 1.0

APTT: 25

ASO: 72 (WNL)

Additional Labs

- C-diff toxin negative
- ANA, Rheumatoid Factor, Anti-SSA and Anti-SSB negative

- **Urine histamine 122 µg/24 hours (normal: 5-42 µg/24 hours)**
- **Serum tryptase 154 (normal: <11)**

Differential Diagnosis

- Inflammatory Bowel Disease (IBD)
- Irritable Bowel Disease(IBS)
- Malabsorption
- Myeloproliferative Disease
- Hereditary/Acquired Angioedema
- Carcinoid Syndrome
- Pheochromocytoma
- Vasoactive intestinal peptide-secreting tumors
- Metastatic disease to bone
- Chronic Idiopathic Urticaria
- Idiopathic Anaphylaxis
- Mast Cell Activation Syndrome
- Systemic Mastocytosis

IBD, IBS, Malabsorption

- IBD/IBS:
  - Abdominal pain
  - Cramping
  - Nausea and vomiting
  - Diarrhea
  - GERD symptoms
- Malabsorption
  - Diarrhea
  - Cramps

Myeloproliferative Disease

- Cellular proliferation of one or more hemotologic cell lines
- Diseases include:
  - Chronic myelogenous leukemia (CML)
  - Essential thrombocytopenia
  - Agnogenic myeloid metaplasia/myelofibrosis
  - Polycythemia vera
  - Chronic idiopathic myelofibrosis
  - Chronic neutrophilic leukemia
  - Chronic eosinophilic leukemia/hypereosinophilic syndrome
- Signs and Symptoms
  - Abdominal discomfort, anemia, coagulopathy, splenomegaly

Hereditary/Acquired Angioedema

- Deficiency of C1 inhibitor
  - low or dysfunctional
- Easy Screen
  - Low C4
- Laryngeal edema unusual in mastocytosis
- NO hives or pruritus seen

Carcinoid Syndrome

- Flushing and diarrhea
- Elevated 24-hour urine 5-HIAA
- NO urticaria, angioedema, but occasional pruritis

Pheochromocytoma

- Flushing, paroxysmal episodes of hypertension
- Mastocytosis associated with hypotension during acute episode of mast cell degranulation
- NO pruritus, angioedema, or urticaria

Vasoactive intestinal peptide-secreting tumors

- Flushing and diarrhea
- Increased levels of VIP
- NO pruritis, angioedema, or urticaria

Chronic Idiopathic Urticaria

- Symptoms >6 weeks duration
  - Pruritis
  - Hives
  - Rash
  - Throaty feeling
  - Absent GI symptoms or other systemic symptoms
- Cyclic presentation/episodic

Idiopathic Anaphylaxis

- Serious allergic reaction without an identifiable trigger
- Signs and symptoms
  - flushing, urticaria, angioedema, wheezing, abdominal pain, vomiting, diarrhea, hypotension
- Must rule out:
  - mastocytosis and C1 esterase inhibitor deficiency/dysfunction first

Mast Cell Activation Syndrome

- Recurrent episodes of anaphylaxis or symptoms resembling allergic reactions
- Provoked by:
  - Medications
    - NSAIDs, contrast agents, neuromuscular blocking agents, antibiotics
  - Infections
  - Hymenoptera stings
  - Surgical procedures
  - Physical stimuli
    - exercise, massage, extreme temperature or sudden temperature changes

Why is this mastocytosis?

- Diarrhea
- Vomiting
- Urticaria
- Flushing
- Atypical skin findings
- Requirement for fluid resuscitation
- Continual symptoms with severe episodes
- Highly elevated tryptase and histamine that remain positive even without episodes

Mastocytosis

- Disorder with mast cell proliferation and infiltration of mast cells into various tissues including:
  - Skin
  - Bone marrow
  - GI tract
  - Liver
  - Spleen

Skin Findings

Urticaria Pigmentosa

Mastocytosis

- Can occur with mast cells in isolation in the skin (cutaneous form) or have organ involvement with indolent presentation
- Most common systemic symptoms include:
  - Anemia
  - Abdominal Pain
  - Diarrhea, nausea, vomiting
  - GERD
  - Pruritis/flushing

Mastocytosis (continued)

- Signs may include:
  - Hepatomegaly
  - Splenomegaly
  - Lymphadenopathy
  - Urticaria
  - Bone pain from osteolysis, rarely pathologic fractures

Mastocytosis (continued)

- Major diagnostic criteria show mast cell infiltration of the bone marrow or extracutaneous tissues

Bone Marrow

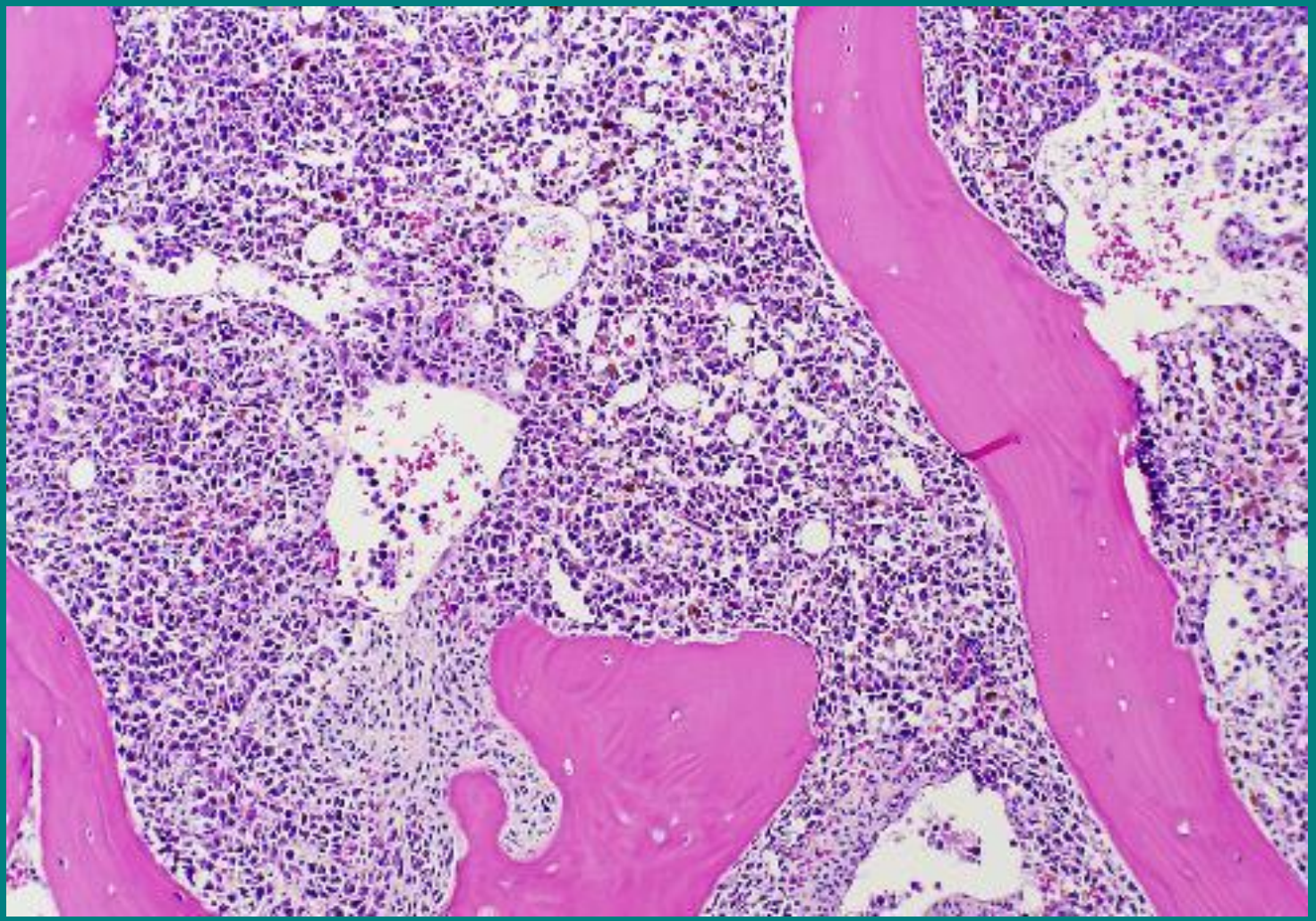


TABLE II. WHO classification of mastocytosis

Variants and subvariants	Abbreviation
Cutaneous mastocytosis	CM
Maculopapular CM*	MPCM
Diffuse CM	DCM
Mastocytoma of skin	
Indolent systemic mastocytosis	ISM
Smoldering SM	SSM
Isolated bone marrow mastocytosis	BMM
Systemic mastocytosis with an associated clonal hematologic non−MC lineage disease	SM-AHNMD†
Aggressive systemic mastocytosis	ASM
With eosinophilia‡	
Mast cell leukemia	MCL
Aleukemic MCL§	
Mast cell sarcoma	MCS
Extracutaneous mastocytoma	

*Also termed urticaria pigmentosa.
†The subtype of the AHNMD has to be defined by WHO criteria as well.
‡In a subgroup of these patients, the *FIPL1-PDGFRA* fusion gene is detectable.
§In these patients circulating MCs are less than 10%.

Valent P, et al. J Allergy Clin Immunol. 2004;114:3-11

TABLE I. WHO criteria for the diagnosis of SM: Criteria

Major*	Multifocal dense infiltrates of MCs in bone marrow or other extracutaneous organs (>15 MCs aggregating)
Minor*	a. MCs in bone marrow or other extracutaneous organs show an abnormal (spindling) morphology (>25%)
	b. Codon 816 *c-kit* mutation D816V in extracutaneous organs†
	c. MCs in the bone marrow express CD2, CD25, or both
	d. Serum tryptase >20 ng/mL (does not count in patients who have an associated hematopoietic clonal non−MC lineage disease (= AHNMD)

*If at least one major and one minor criterion or 3 minor criteria are fulfilled, the diagnosis of SM can be established.

†Other activating mutations at codon 816 of *c-kit* also count as a minor criterion.

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TABLE IV. Practical guide for the diagnostic evaluation of patients with suspected mastocytosis

Initial sign-symptom	Recommended diagnostic procedures
UP-like skin lesions in pediatric cases	1. Skin biopsy (with analysis of *c-kit* D816V) and serum tryptase*
UP-like skin lesions in adult patients	1. Bone marrow examinations, skin biopsy, and serum tryptase (>20 ng/mL in most SM cases) 2. In case of SM → complete staging: GI tract, x-ray of bones, ultrasound of abdomen, complete blood count, chemistry, coagulation parameters, *c-kit* mutation status
Mediator-related symptoms but no skin lesions (UP)†	1. Serum tryptase, if >20 ng/mL → 2. 2. Bone marrow examination, if SM → 3. 3. SM—staging†
Severe unexplained allergic or anaphylactoid reaction	1. Serum tryptase, if >20 ng/mL → 2. 2. Repeat serum tryptase a few weeks later: if then, serum tryptase is >20 ng/mL → 3. 3. Bone marrow examination, if SM → 4. 4. SM—staging†

UP, Urticaria pigmentosa.

*Because of a different ratio (ie, MC granule volume/whole body volume in young infants [compared with adults]), a serum tryptase level slightly exceeding 20 ng/mL in these young patients might not be regarded as an indicator for SM. Therefore it is recommended to monitor the serum tryptase level over time but do not perform a bone marrow puncture unless other signs for a systemic hematologic disease are found (organomegaly, osteolyses, severe cytopenias, or others).

†Especially in patients with aggressive MC disorders, skin lesions are absent. Therefore it is of pivotal importance to know the subtype of SM in these patients as soon as possible. In aggressive SM the serum tryptase level is usually higher than in patients with isolated bone marrow mastocytosis (often <20 ng/mL), a benign MC disease in which skin lesions are also absent.

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TABLE V. Cytoreductive therapy in SM

Disease variant	Treatment options
Typical indolent systemic mastocytosis (ISM)	No cytoreductive treatment required (exception: consider IFN-α2b for severe osteoporosis, even if no histology documenting ASM is available).
Smoldering systemic mastocytosis (SSM)	Watch and wait in most cases. However, in select cases (eg, progressive organomegaly) IFN-α2b ± glucocorticoids can be considered.
SM-AHNMD	Treat AHNMD as if no SM is present and also treat SM as if no AHNMD was found. If splenomegaly and hypersplenism prohibit therapy, consider splenectomy.
Aggressive systemic mastocytosis (ASM)	IFN-α2b ± glucocorticoids or cladribine. If splenomegaly and hypersplenism prohibit with slow progression therapy, consider splenectomy.
ASM: rapid progression† and patients who do not respond to IFN-α2b	Polychemotherapy (± IFN-α2b) or cladribine; bone marrow transplantation for select cases. If splenomegaly and hypersplenism prohibit therapy, consider splenectomy.
ASM without *c-kit* D816V or with the *FIPL1-PDGFRA* fusion gene (+ eosinophilia)	Consider STI571 (Imatinib) therapy as an alternative treatment approach.
Mast cell leukemia (MCL)	Polychemotherapy or cladribine (± IFN-α2b). Consider bone marrow transplantation. If splenomegaly and hypersplenism prohibit therapy, consider splenectomy. Consider hydroxyurea as palliative drug.

SM-AHNMD, Systemic mastocytosis with an associated hematologic clonal non—MC lineage disease.

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Systemic Mastocytosis Management Objectives

- Basic Treatment of Systemic Mastocytosis
- Common Triggers Medications
- Medical Emergency Response Plan for Systemic Mastocytosis
- Current patient…where are we at

Basic Treatment of Systemic Mastocytosis

- H1 and H2 antihistamines
- Sodium cromolyn
- LTE4 receptor antagonist
- Aspirin if tolerated
- Avoiding mast cell degranulating agents
- Proton Pump inhibitors
- Anticholinergics
- Epinephrine
- Oral Steroids

Common Triggers

- Medications
- Physical Stimuli
- Emotional Factors
- Alcoholic beverages

Medical Emergency Response

- Epi
  - Repeat Q 5minutes if needed
- Call 911 after first epi
- Diphenhydramine
- Oxygen
- IV fluids
- Albuterol if needed

Current patient…initial prescription

- Gastrograffin (Sodium cromolyn)
  - stabilizes gut mast cells
- Singulair
- Cyclosporin
- Ranitidine
- Cyproheptadine

Current Patient-Imaging/consults/labs

- Ultrasound of abdomen-Splenomegaly
- Labs-repeat tryptase, CBCdiff
- Consults: hematology/oncology
  - to complete her workup
    - bone marrow biopsy for:
      - certain mutations (Ckit)
      - progression of malignancy
      - show mast cell infiltration

Follow-up

- Patient had elevated blood pressure
  - Cyclosporine never started
- Patient unable to attend bone marrow biopsy
- Phone follow up noted no further episodes

Is it Systemic Mastocytosis?

- Most likely yes
  - Continual symptoms with severe episodes
  - Elevated tryptase both in episode and while well
  - Elevated urine histamine

Conclusion

- While there is no cure for this disorder, medications can be used to treat the symptoms
- Those with systemic involvement have a poor prognosis

Further Reading

- Valent P, et al. J Allergy Clin Immunol. 2004;114:3-11
- The Mastocytosis Society
  - http://www.tmsforacure.org/welcome.php

QUESTIONS