Mast Cell Disorders and Mastocytosis

Pathophysiology, Diagnosis & Management

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Mast Cell Biology:

Development & Immune Dynamics

Origin & Differentiation

- Derived from $CD34^+$ hematopoietic stem cells in bone marrow
- Migrate to peripheral tissues in response to Stem Cell Factor (SCF)
- SCF binds KIT receptor (CD117) → critical for:

✓Proliferation

✓Maturation

✓Migration

✓Survival of mast cells

- ***Tissue microenvironment (blood vessels, nerves, cytokines) modulates local mast cell phenotype and function***

Tissue Distribution & Phenotypes

- Tissue-resident cells in:

✓Skin

✓Lungs

✓Gastrointestinal mucosa

- Phenotypic subtypes:
- MC_T (tryptase$^+$ only) – mucosal
- MC_{TC} (tryptase$^+$ + chymase$^+$) – connective tissue

Phenotypic Subtypes of Mast Cells

Mast cells are functionally and phenotypically diverse depending on their tissue localization and enzyme expression profiles. The two most well-characterized subtypes in humans are:

MC_T — Tryptase-positive only (Mucosal Mast Cells)

- Express only tryptase, a serine protease stored in granules
- Found predominantly in **mucosal tissues**, such as:

✓ Respiratory tract

✓ Gastrointestinal mucosa

- **Clinical relevance:**

✓ IgE-dependent allergic responses (e.g., allergic rhinitis, food allergy)

✓ Highly responsive to aeroallergens and food antigens

✓ Often increased in asthma and eosinophilic esophagitis

MC_{TC} — Tryptase and Chymase-positive (Connective Tissue Mast Cells)

- Contain both tryptase and chymase, plus other proteases like carboxypeptidase A
- Reside in **connective tissues**, especially:

✓ Skin

✓ Submucosa

✓ Perivascular and perineural spaces

- **Clinical relevance:**

✓ Involved in chronic inflammation, fibrosis, and tissue remodeling

✓ Major subtype in cutaneous mastocytosis and Systemic Mastocytosis

✓ More resistant to degranulation compared to MC_T

Summary Table:

Subtype	Proteases	Location	Clinical Importance
MCT	Tryptase only	Mucosal tissues	Allergic rhinitis, asthma, food allergy
MCTC	Tryptase + Chymase	Skin, connective tissue	Mastocytosis, chronic inflammation

Key Surface Receptors

Receptor	Function
FcεRI	High-affinity IgE receptor → triggers degranulation on allergen cross-linking
KIT (CD117)	Binds SCF → essential for MC development
C3a/C5a (anaphylatoxins); Neuropeptides (CRH, Substance P, neurotensin); Cytokines (IL-33); Toll-like receptors (TLRs) – detect microbial signals	

Functions Beyond Allergy

Role	***Mediators Released***
Allergy & Anaphylaxis	Histamine, Tryptase, Leukotrienes
Wound Healing	VEGF, TNF
Neuroinflammation	Substance P, IL-33
Immune Modulation	IL-6, IL-13, TGF-β
Antimicrobial Defense	ROS, cytokines, TLR ligands

Clinical Insight

- Mast cells are not exclusively IgE-driven.
- They respond to:

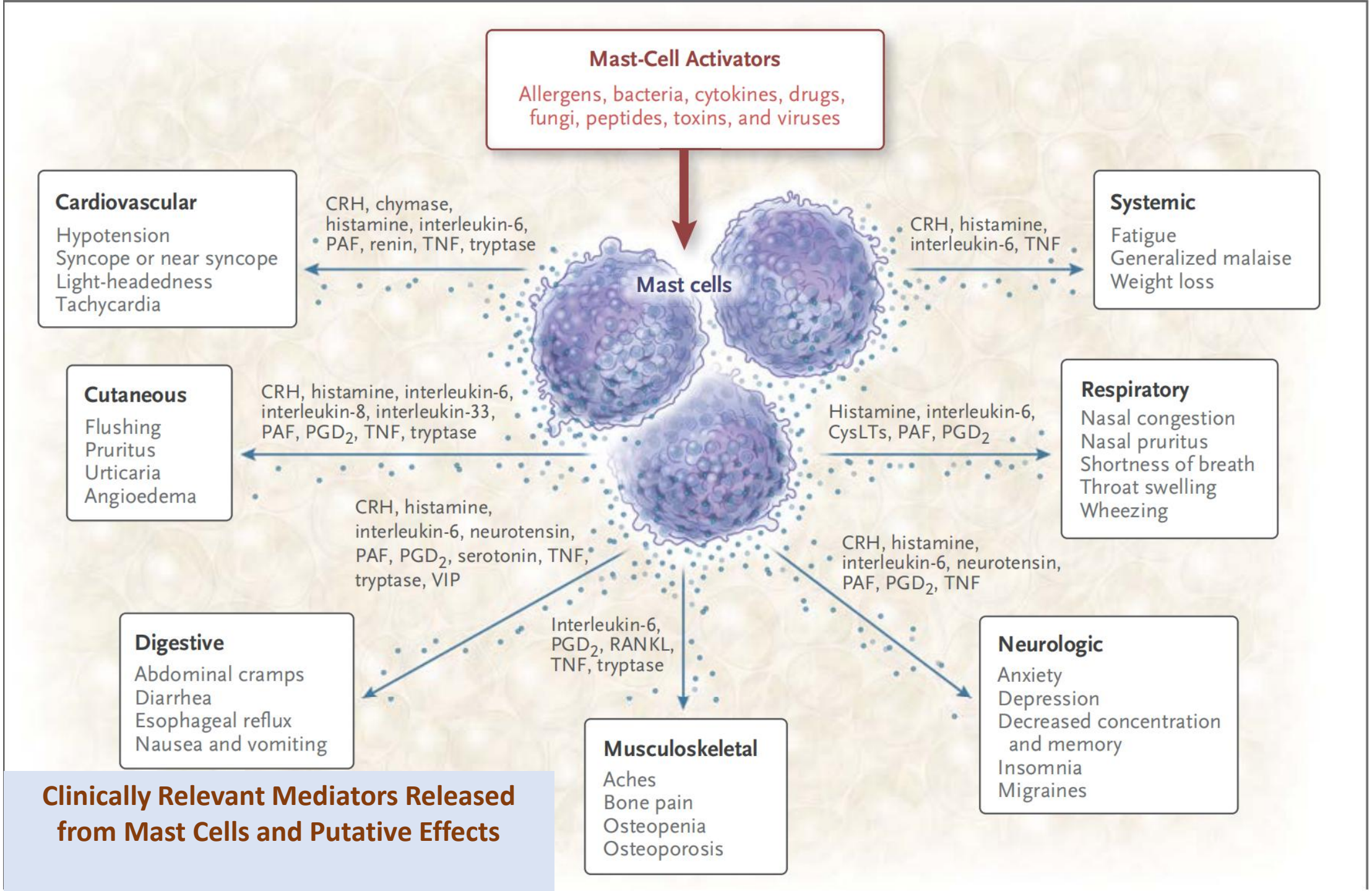
✓Emotional stress (via CRH)

✓Drugs

✓Infections

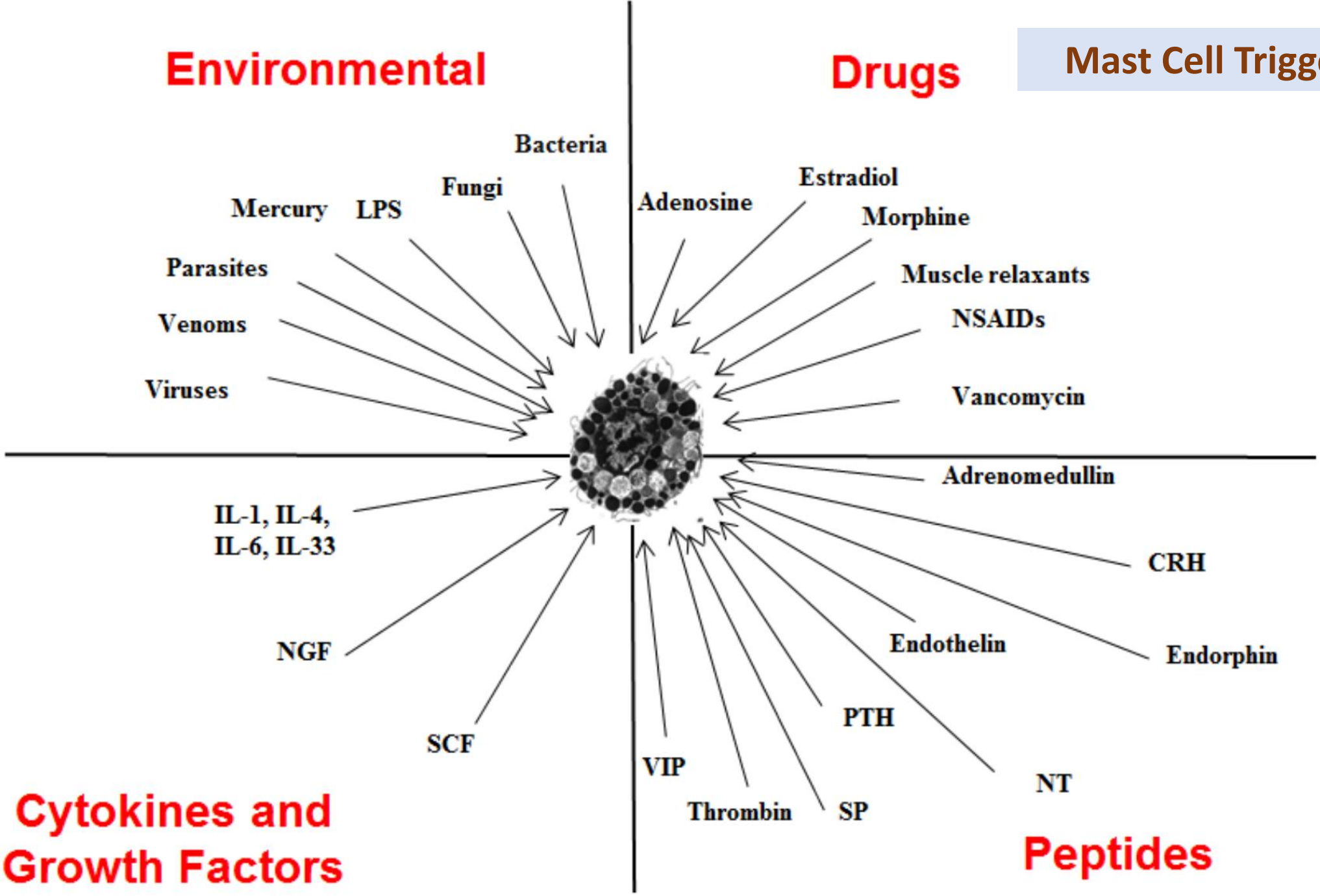
✓Physical triggers

- ***Such non-IgE-mediated activation is clinically critical in Systemic Mastocytosis and Mast Cell Activation Syndromes.***



Clinically Relevant Mediators Released from Mast Cells and Putative Effects

Mast Cell Triggers



KIT

Pathophysiology & Mutations

What is KIT?

- KIT (CD117) is a type III receptor tyrosine kinase
- Encoded by the KIT gene on chromosome 4q12
- Expressed on mast cells, hematopoietic stem cells, melanocytes, and germ cells
- Ligand: Stem Cell Factor (SCF)
- → SCF binding → dimerization → autophosphorylation → downstream signaling (PI3K, MAPK, JAK/STAT)

Oncogenic KIT Mutations in Mastocytosis

Mutation	Effect	Clinical Relevance
D816V (Exon 17)	Ligand-independent activation	~90% of SM patients
V560G (Juxtamembrane)	Gain-of-function	Rare
K509I	Gain-of-function	Found in pediatric cases
D816H/Y/F	Variants of D816	Aggressive subtypes
KIT-negative SM	Check for: TPSAB1 CNV, PDGFRA fusion	Consider other neoplasms

KIT-Independent Mutations

(Important in Differential Dx)

- FIP1L1-PDGFRA fusion → Eosinophilic myeloproliferative disorders
- PRKG2-PDGFRB fusion → Myeloid neoplasms with MC involvement
- These mimic SM but are responsive to imatinib, unlike D816V^{+} SM.

Clinical Key Point

- The D816V mutation leads to constitutive KIT activation, promoting:

✓Uncontrolled mast cell proliferation

✓Mediator release

✓Therapeutic resistance to imatinib

- Mutation detection (AS-PCR or digital PCR) is essential for diagnosis, prognosis, and therapy selection.

Targeted therapies like ***avapritinib*** and ***midostaurin*** are designed to inhibit KIT D816V. This mutation is a cornerstone in both the classification and management of systemic mastocytosis.

Mast Cell Disorders

Classification

1. Cutaneous Mastocytosis (CM)

- Primarily skin-limited mast cell proliferation
- Common in children; often self-limiting

Subtype	Description
UP/MPCM (Urticaria Pigmentosa / Maculopapular CM)	Most common form
DCM (Diffuse Cutaneous Mastocytosis)	Extensive skin thickening, blistering
Solitary Mastocytoma	Single lesion, often in infants

2. Systemic Mastocytosis (SM)

- Multisystem mast cell infiltration – per WHO 2016 & ECNM criteria

Subtype	Description
ISM (Indolent SM)	Skin + mild systemic symptoms
SSM (Smoldering SM)	Higher MC burden but no organ failure
ASM (Aggressive SM)	Organ dysfunction without other hematologic neoplasm
SM-AHN	SM + associated hematologic neoplasm (e.g., MDS, CMML)
MCL (Mast Cell Leukemia)	Rare, leukemic variant; poor prognosis

3. Mast Cell Activation Syndromes (MCAS)

- Clinical signs of mast cell mediator release without overt proliferation

Type	Mechanism
Primary (Clonal MCAS)	KIT mutation + abnormal MCs
Secondary MCAS	IgE-mediated allergies, infections, etc.
Idiopathic MCAS	No identifiable driver; diagnosis of exclusion

4. Hereditary α-Tryptasemia (HaT)

- Genetic disorder → ↑ TPSAB1 copy number
- Elevated basal serum tryptase levels
- May coexist with MCAS or SM
- Symptoms: flushing, anaphylaxis, GI dysfunction, POTS

Proper classification guides risk stratification, genetic testing, and therapeutic decisions — particularly distinguishing between indolent and aggressive systemic forms, or diagnosing MCAS versus SM.

1. **MASTOCYTOSIS**
   - a. **Cutaneous Mastocytosis ***
     - i. Diffuse cutaneous mastocytosis
     - ii. Maculopapular mastocytosis (Urticaria Pigmentosa)
     - iii. Cutaneous mastocytoma
   - b. **Systemic Mastocytosis ***
     - i. Indolent systemic mastocytosis (ISM) [includes bone marrow mastocytosis]
     - ii. Smoldering systemic mastocytosis (SSM)
   - c. **Advanced Systemic Mastocytosis ***
     - i. Aggressive systemic mastocytosis (ASM)
     - ii. Mastocytosis with associated hematological neoplasia (SM-AHN)
     - iii. Mast cell leukemia (including aleukemic leukemia)
   - d. **Nonclonal disorders: Mast cell sarcoma**
2. **MAST CELL ACTIVATION SYNDROME (MCAS)**
   - a. **Primary Mast cell Activating Syndrome/Monoclonal Mast Cell Activating Syndrome (MMAS)/Clonal Mast Cell Activating Syndrome (CMCAS) ***
   - b. **Secondary Mast Cell Activating Syndrome** (IgE-mediated allergy, autoim-munity, chronic infection, nematode infestation, underlying neoplasia)
   - c. **Idiopathic Mast Cell Activation Syndrome** (no obvious etiology)
   - d. **Combined primary disorder with allergy-triggered mast cell activation**
3. **IDIOPATHIC ANAPHYLAXIS (IA)**
   - a. No obvious allergens (cryptic allergens and mammalian meat allergy to be excluded)
   - b. Idiopathic anaphylaxis associated with bone marrow mastocytosis and clon-ality *
   - c. IA associated with CMCAS and/or hereditary alpha-tryptasemia *
4. **REACTIONS TO HYMENOPTERA VENOM AND CLONAL MAST CELL DIS-EASE**
   - a. Associated with bone marrow mastocytosis and clonality *
   - b. Associated with MCAS and/or clonality *
5. **BONE MARROW MASTOCYTOSIS**
6. **HEREDITARY ALPHA TRYPTASEMIA**
   - a. Isolated condition
   - b. Associated with CMCAS, SM and variants and IA
7. **COMBINED DISORDERS** (Various combination of above conditions)

Clinical Manifestations of
Mast Cell Disorders

System	Key Symptoms
Skin	• Urticaria pigmentosa (maculopapular rash)

- Gastrointestinal: Cramping; Diarrhea; Acid hypersecretion; Peptic ulcers
- Bone: Osteopenia; Pathological fractures
- Neurological: Headaches; Brain fog (cognitive slowing)
- Cardiovascular: Hypotension; Anaphylaxis; Syncope
- Liver/Spleen: Hepatomegaly; Elevated ALP, GGT; Fibrosis

Conditions That Can Mimic
Mast-Cell Disorders

Cardiac conditions

Coronary hypersensitivity (the Kounis syndrome)*
Postural orthostatic tachycardia syndrome

Endocrine conditions

Fibromyalgia
Parathyroid tumor
Pheochromocytoma
Carcinoid syndrome

Digestive conditions

Adverse reaction to food*
Eosinophilic esophagitis*
Eosinophilic gastroenteritis*
Gastroesophageal reflux disease
Gluten enteropathy
Irritable bowel syndrome
Vasoactive intestinal peptide–secreting tumor

Immunologic conditions

Autoinflammatory disorders such as deficiency of interleukin-1–receptor antagonist*
Familial hyper-IgE syndrome
Vasculitis*

Neurologic and psychiatric conditions

Anxiety
Chronic fatigue syndrome
Depression
Headaches
Mixed organic brain syndrome
Somatization disorder
Autonomic dysfunction
Multiple sclerosis

Skin conditions

Angioedema*
Atopic dermatitis*
Chronic urticaria*
Scleroderma*

* Localized mast-cell activation can occur.

Clinical Pearl

- Symptom severity often correlates with:

✓Mast cell burden (infiltration into tissue)

✓Mediator release (e.g., histamine, tryptase, leukotrienes)

- Baseline tryptase can support diagnosis, but:

✓It does not always correlate with severity

✓It may be normal in MCAS or HaT

Key Clinical Insight:

- Symptoms are often nonspecific, mimicking:

✓IBS, anxiety, allergic rhinitis, chronic fatigue, fibromyalgia

- ***A high index of suspicion is needed in multisystem, episodic cases***

Diagnostic Algorithm

Mast Cell Disorders

WHO Diagnostic Criteria for Systemic Mastocytosis

Major Criterion

- Multifocal dense infiltrates of ≥15 mast cells in bone marrow or extracutaneous tissues

(e.g., GI mucosa, liver, spleen)

Minor Criteria (≥1 Major + 1 Minor OR ≥3 Minor = SM)

- **Atypical Mast Cell Morphology:** Spindle-shaped, hypogranulated in marrow/biopsy
- **KIT D816V Mutation:** Detected via AS-PCR or digital PCR)
- **Aberrant Surface Markers:** MCs express CD2 and/or CD25
- **Elevated Serum Tryptase**

>20 ng/mL persistently in the absence of other myeloid neoplasm)

Box 1. Criteria for Diagnosis of Systemic Mastocytosis.

Systemic mastocytosis (SM)/Indolent Systemic Mastocytosis (ISM)
Diagnosis is confirmed if patient expresses one major criterion and one minor criterion or expresses three minor criteria

Major criteria:
Multifocal dense infiltrates of mast cells (>15 cells/aggregate) in bone marrow or extramedullary, extracutaneous tissue

Minor criteria:

1. >25% of infiltrating mast cells are atypical or spindle-shaped
2. KIT mutation in bone marrow or peripheral blood or extracutaneous tissue
    a. Other rarer mutations may be observed
    b. These include TET2, SRSF2, ASXL1, RUNX1, CBL, JAK2
3. Mast cells express clonal markers such as CD25 or CD2 by immunocytochemistry or flow cytometry (besides CD117 or tryptase)
4. Serum tryptase is >20 ng/mL (unless there is an underlying myeloid neoplasm)

Diagnostic Workup Tools

Test	Purpose
Serum Tryptase (baseline + episodic)	Marker of mast cell burden & activation
Bone Marrow Biopsy	Confirms dense MC clusters + morphology
KIT Mutation Analysis	PCR/digital PCR for D816V & other mutations
Immunophenotyping	CD117, CD25, CD2 by flow cytometry
TPSAB1 Gene Testing	To detect Hereditary Alpha Tryptasemia (HaT)

Clinical Aid: REMA Score

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JUNE 2010

VARIABLE		SCORE
GENDER	Male	+1
	Female	-1
CLINICAL SYMPTOMS	Absence of urticaria and angioedema	+1
	Urticaria and/or angioedema	-2
	Presyncope and/or syncope	+3
TRYPTASE*	<15 ng/mL	-1
	>25 ng/mL	+2

*Baseline serum tryptase

SCORE < 2: low probability of clonal MCAD

SCORE ≥ 2: high probability of clonal MCAD

Key Takeaways:

- Diagnosis hinges on combining histologic, molecular, and clinical data
- Molecular testing (e.g., KIT D816V) is essential for precision treatment
- HaT and MCAS require exclusion before confirming SM

What is MCAS?

Mast Cell Activation Syndrome (MCAS) refers to episodic systemic symptoms due to inappropriate mast cell activation, often without overt mast cell proliferation (i.e., not SM).

Consensus Diagnostic Criteria

(All 3 criteria must be met)

- **Episodic symptoms involving ≥2 organ systems, such as:**

✓Skin (flushing, itching)

✓GI (cramping, diarrhea)

✓Cardiovascular (hypotension, tachycardia)

✓Respiratory (wheezing, throat tightness)

✓Neuropsychiatric (brain fog, headaches)

- **Biochemical confirmation:**

✓Serum tryptase elevation during episode

✓Must follow “20% + 2 rule”:

✓Tryptase level during event must exceed:

✓(Baseline x 1.2) + 2 ng/mL

- **Clinical improvement with mast cell-directed therapy**

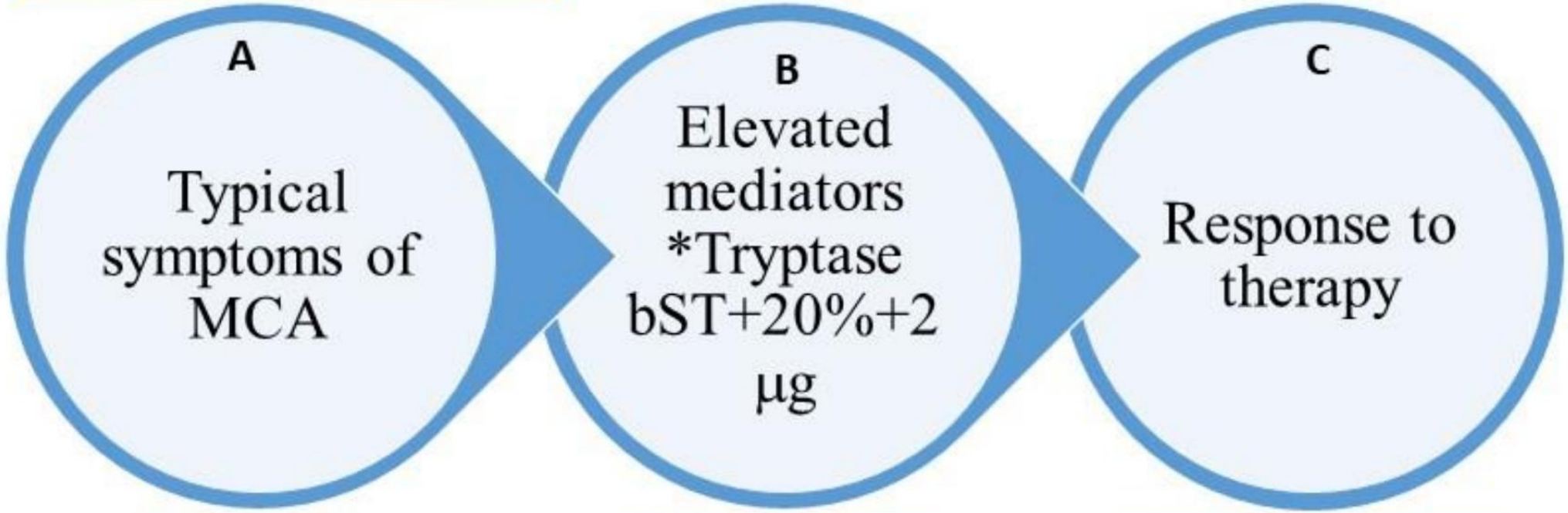
✓H1/H2 antihistamines, cromolyn, leukotriene antagonists, anti-IgE (omalizumab)

MCAS: Criteria for diagnosis

Symptoms of mediator release

Presence of KIT mutations defines clonality—but surrogate markers such as CD25 or CD2 by immunostaining or flow cytometry can be used to define clonality of mast cells

Acute onset of symptoms involves at least 2 systems



Tryptase*
Histamine
Prostaglandins
Leukotrienes

Antihistamines
PG inhibitors
LT inhibitors
Cromolyn sodium

MCAS Classification

Type	Features
Clonal MCAS	KIT mutation present; may be indolent SM variant
Secondary MCAS	Triggered by allergies (IgE), infections, autoimmune disease
Idiopathic MCAS	Meets criteria but no trigger or clonality identified

Clinical Insight

- MCAS is underdiagnosed. It often mimics:

✓Allergies

✓IBS

✓POTS

✓Fibromyalgia

✓Anxiety/panic disorders

- Requires high clinical suspicion and a structured diagnostic approach.

Hereditary Alpha Tryptasemia (HaT)

- Autosomal dominant genetic trait

- Caused by increased copy number of the TPSAB1 gene

→ Encodes α-tryptase, leading to elevated basal serum tryptase

Clinical Features

- Often overlaps with:

✓MCAS (Mast Cell Activation Syndrome)

✓POTS (Postural Orthostatic Tachycardia Syndrome)

✓EDS (Ehlers-Danlos Syndrome)

- Common Symptoms:

✓Episodic flushing, pruritus

✓Syncope, hypotension

✓GI dysmotility: bloating, diarrhea

✓Anaphylaxis (often triggered by stress, heat, or unknown)

Key Diagnostic Insight

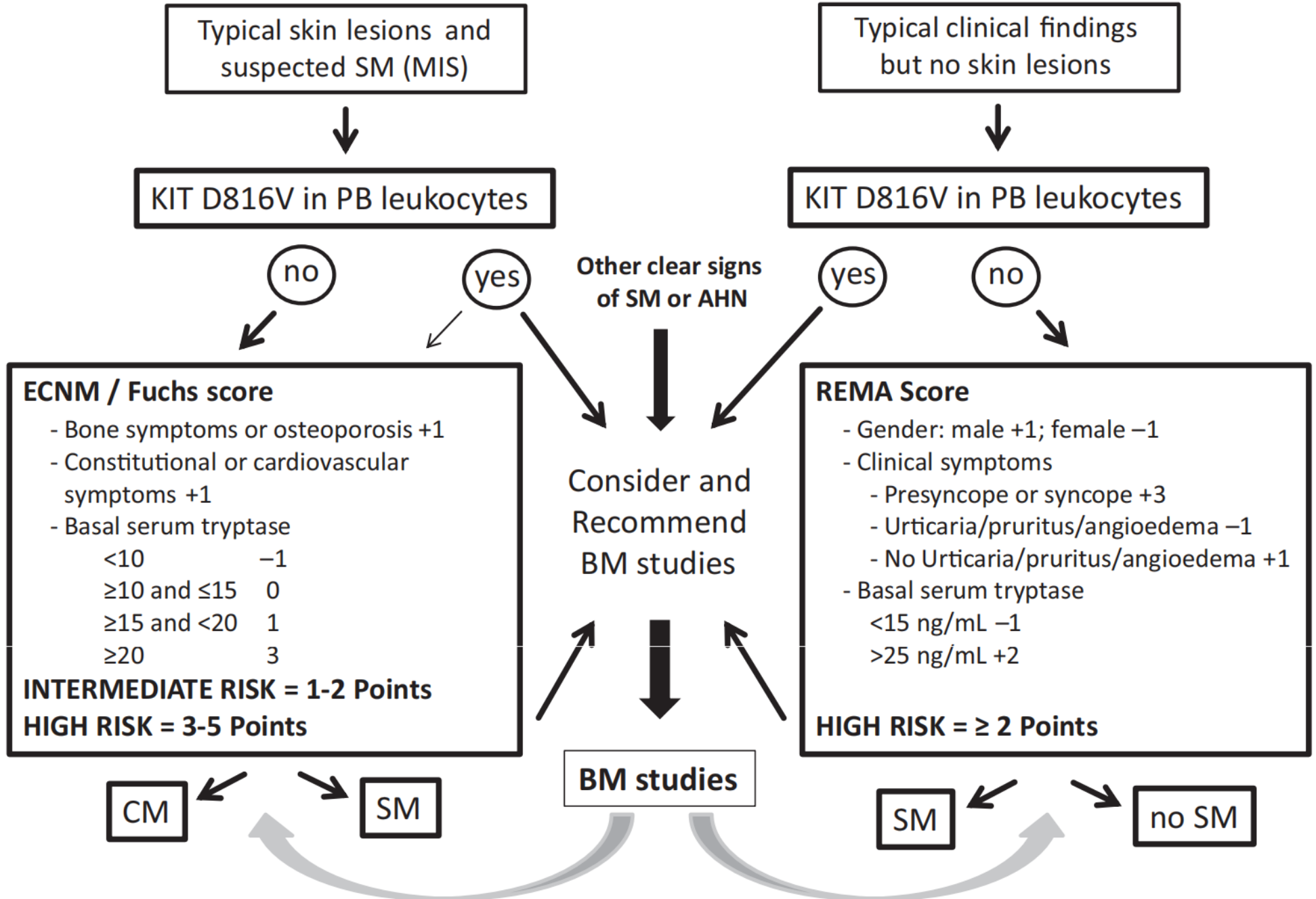
- Consider HaT if:

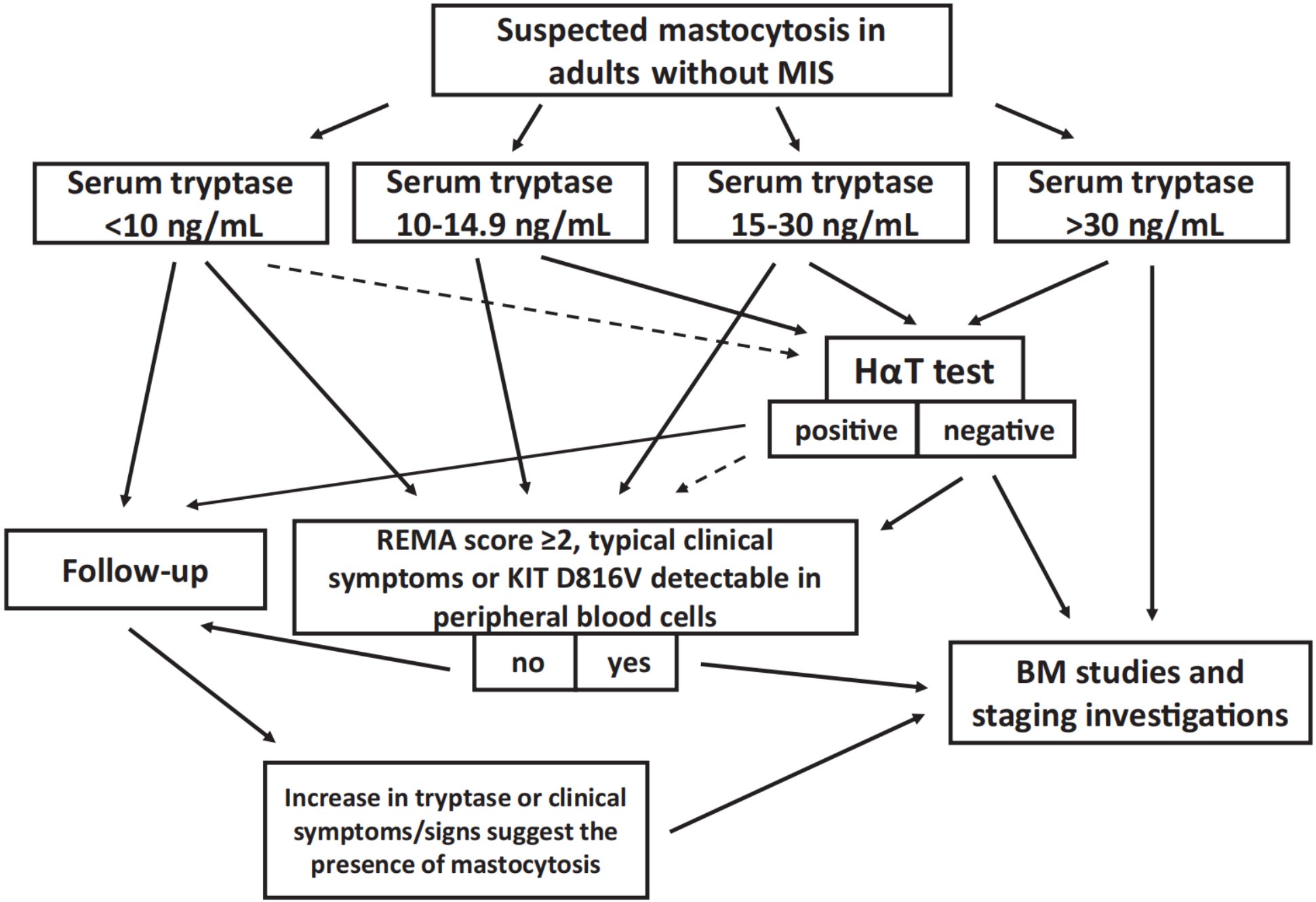
✓Baseline serum tryptase ≥8–10 ng/mL

✓No KIT D816V mutation

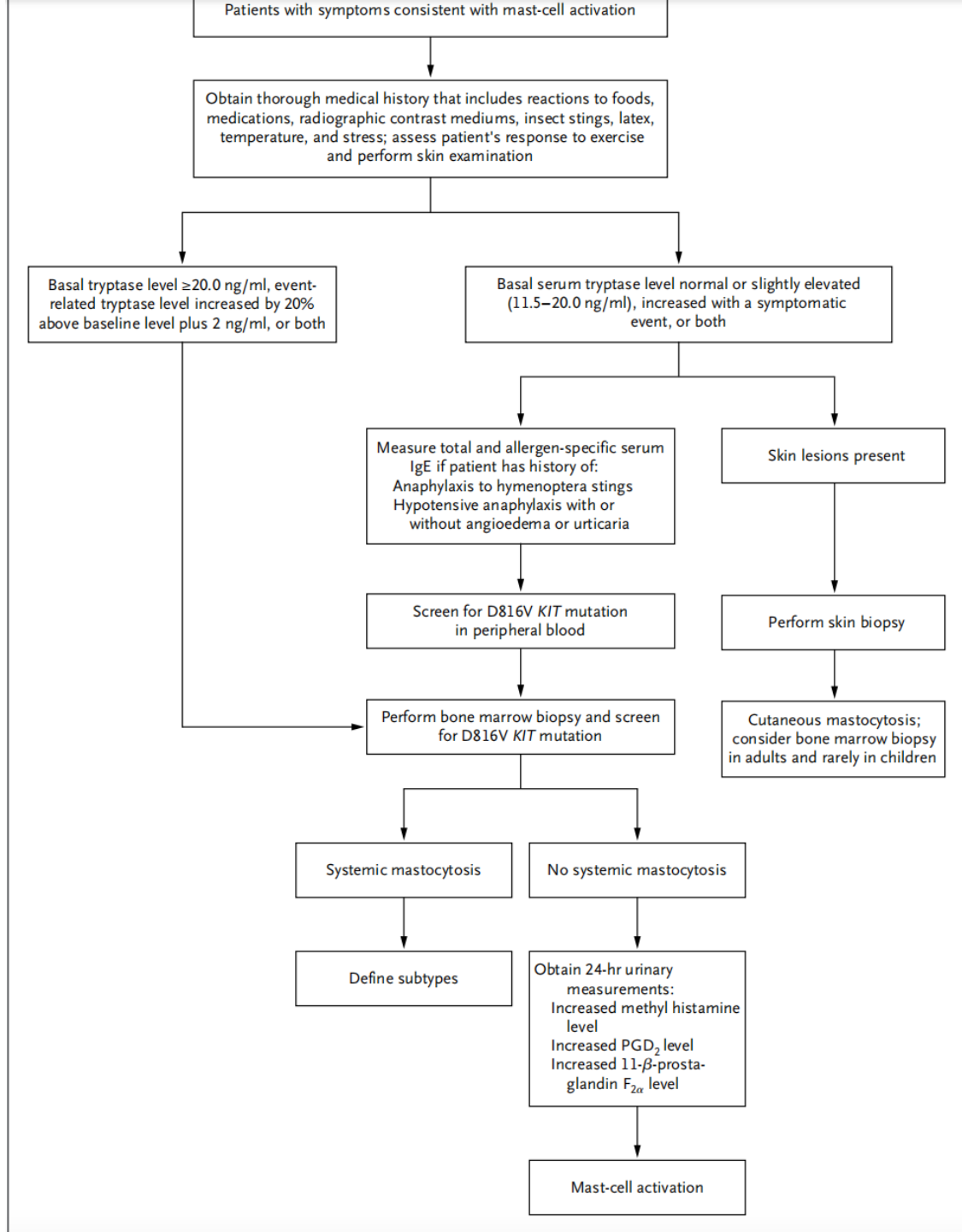
✓Symptoms are multisystem and episodic

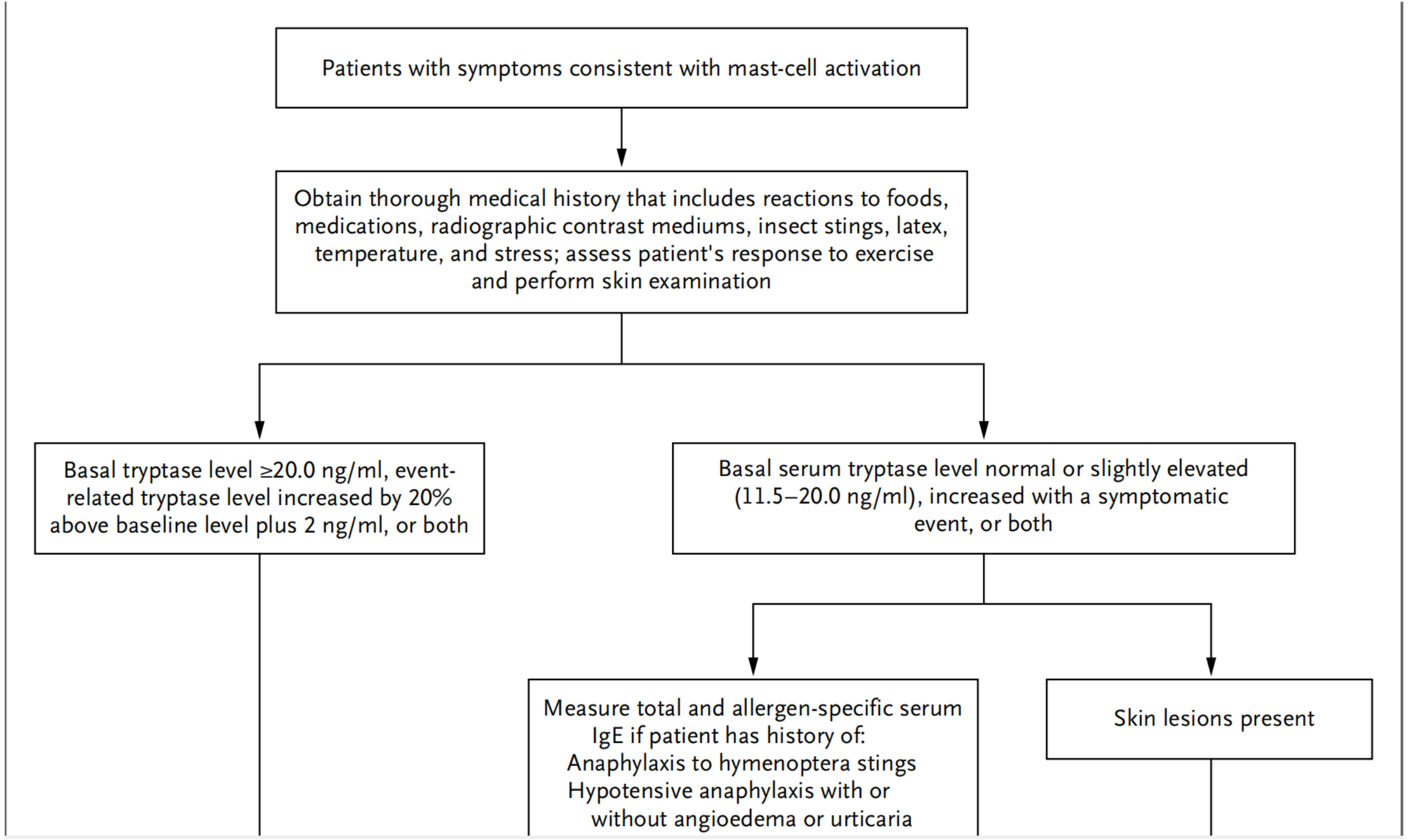
✓Confirm with TPSAB1 gene copy number testing


Typical skin lesions and suspected SM (MIS)
KIT D816V in PB leukocytes
no
yes
ECNM / Fuchs score
- Bone symptoms or osteoporosis +1
- Constitutional or cardiovascular symptoms +1
- Basal serum tryptase
<10 −1
≥10 and ≤15 0
≥15 and <20 1
≥20 3
INTERMEDIATE RISK = 1-2 Points
HIGH RISK = 3-5 Points
CM
SM
Other clear signs of SM or AHN
Consider and Recommend BM studies
BM studies
Typical clinical findings but no skin lesions
KIT D816V in PB leukocytes
yes
no
REMA Score
- Gender: male +1; female −1
- Clinical symptoms
- Presyncope or syncope +3
- Urticaria/pruritus/angioedema −1
- No Urticaria/pruritus/angioedema +1
- Basal serum tryptase
<15 ng/mL −1
>25 ng/mL +2
HIGH RISK = ≥ 2 Points
SM
no SM


Suspected mastocytosis in adults without MIS
Serum tryptase <10 ng/mL
Serum tryptase 10-14.9 ng/mL
Serum tryptase 15-30 ng/mL
Serum tryptase >30 ng/mL
HαT test
positive
negative
Follow-up
REMA score ≥2, typical clinical symptoms or KIT D816V detectable in peripheral blood cells
no
yes
BM studies and staging investigations
Increase in tryptase or clinical symptoms/signs suggest the presence of mastocytosis

Algorithm for Evaluation of Possible Mastocytosis.


Patients with symptoms consistent with mast-cell activation
Obtain thorough medical history that includes reactions to foods, medications, radiographic contrast mediums, insect stings, latex, temperature, and stress; assess patient's response to exercise and perform skin examination
Basal tryptase level ≥20.0 ng/ml, event-related tryptase level increased by 20% above baseline level plus 2 ng/ml, or both
Basal serum tryptase level normal or slightly elevated (11.5–20.0 ng/ml), increased with a symptomatic event, or both
Measure total and allergen-specific serum IgE if patient has history of:
Anaphylaxis to hymenoptera stings
Hypotensive anaphylaxis with or without angioedema or urticaria
Skin lesions present
Screen for D816V *KIT* mutation in peripheral blood
Perform skin biopsy
Perform bone marrow biopsy and screen for D816V *KIT* mutation
Cutaneous mastocytosis; consider bone marrow biopsy in adults and rarely in children
Systemic mastocytosis
No systemic mastocytosis
Define subtypes
Obtain 24-hr urinary measurements:
Increased methyl histamine level
Increased PGD_2 level
Increased 11-β-prostaglandin $F_{2\alpha}$ level
Mast-cell activation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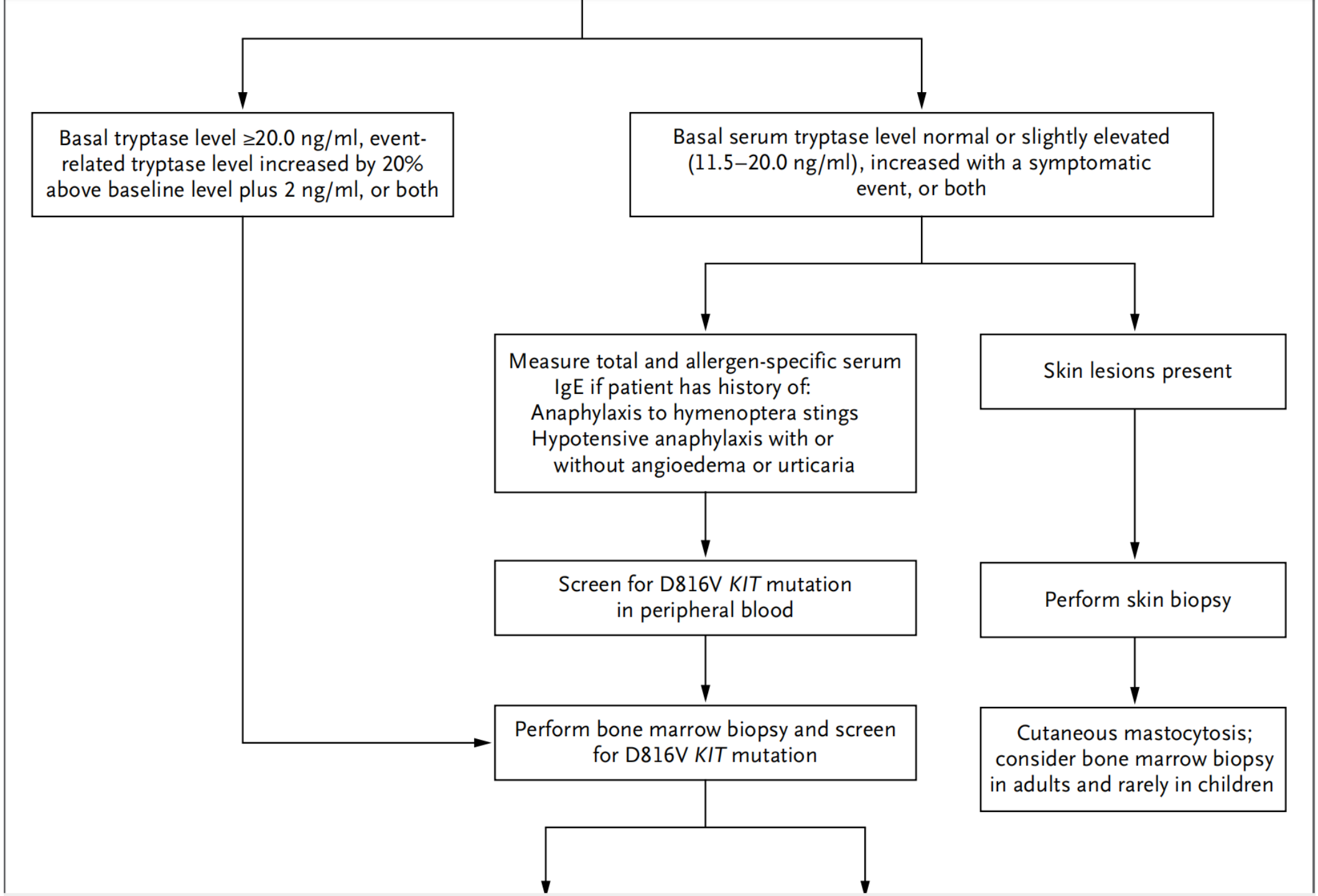
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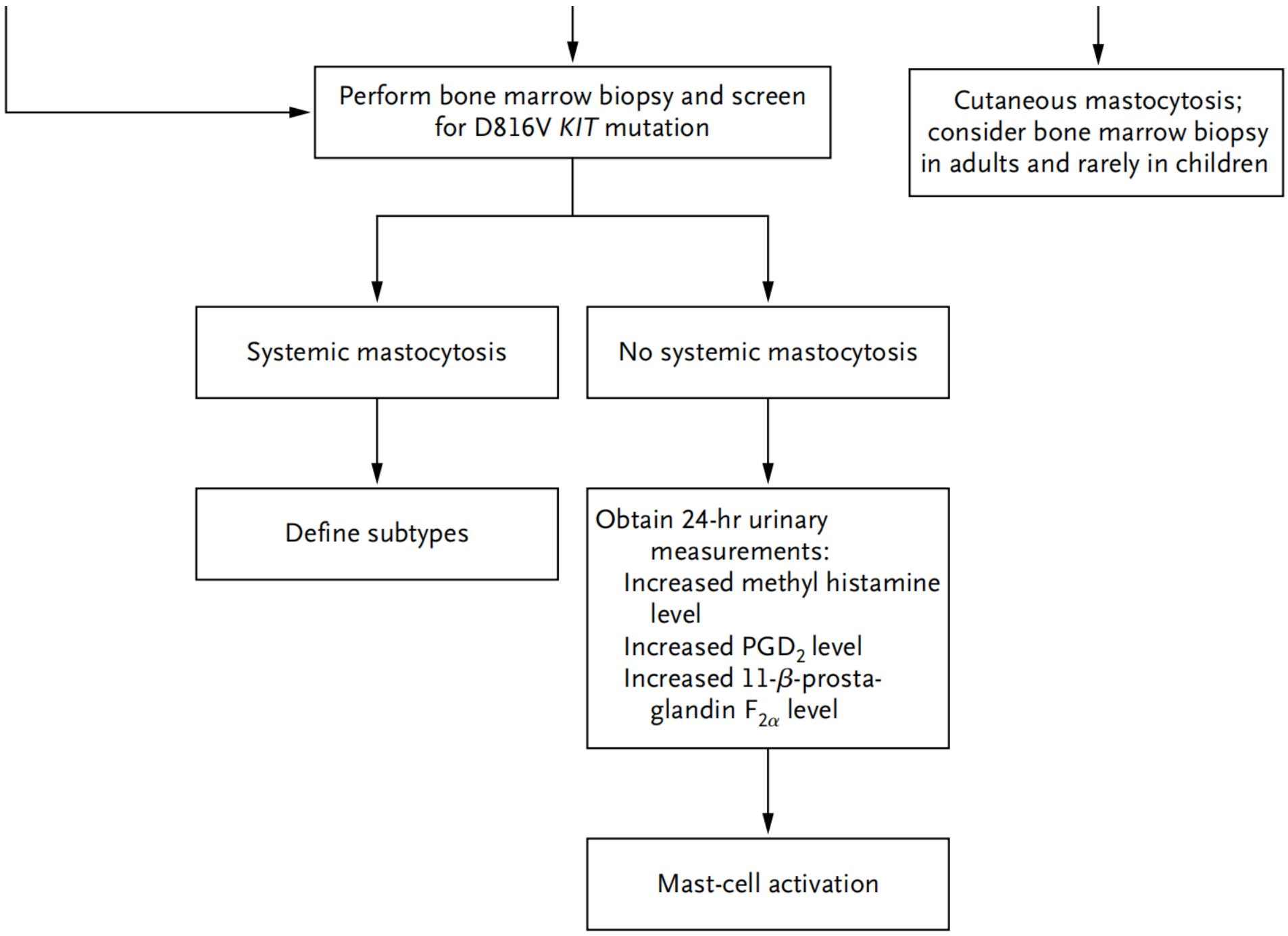
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Mast-cell activation

Management Approach

Mast Cell Disorders

Supportive Management

- H1 Antihistamines: Loratadine, cetirizine – for pruritus, flushing
- H2 Antihistamines: Ranitidine, famotidine – for GI acid symptoms
- Leukotriene Receptor Antagonists: Montelukast – mediator symptom control
- Sodium Cromolyn: Mast cell stabilizer, esp. for GI symptoms
- Epinephrine Auto-injector: For anaphylaxis risk in MCAS/SM
- Topical Corticosteroids: Symptom relief in urticaria pigmentosa / CM

Advanced / Targeted Therapies

- Midostaurin (PKC412):

→ Multikinase inhibitor, blocks D816V KIT

→ Use in AdvSM (e.g., ASM, SM-AHN, MCL)

- Avapritinib:

→ Selective KIT D816V inhibitor

→ Approved for AdvSM; improved mediator symptoms

- Interferon-α2b & Cladribine:

→ Cytoreduction in aggressive or refractory SM

- Allogeneic Bone Marrow Transplant (BMT):

→ Considered in MCL or resistant cases

Trigger Avoidance Is Critical

- **Avoid:**

✓Alcohol

✓NSAIDs

✓Opioids

✓Temperature extremes

✓Stress

✓Radiocontrast agents

Management should be tailored based on phenotype, burden, and risk — integrate supportive + cytoreductive strategies where indicated

Prognosis & Monitoring in Mast Cell Disorders

Prognosis by Subtype

Disorder	Prognosis / Survival
Cutaneous Mastocytosis (CM)	Excellent prognosis
Rare systemic progression	
Indolent Systemic Mastocytosis (ISM)	Chronic course, normal life expectancy
But: Symptom burden & QoL often affected	
SM with Associated Hematologic Neoplasm (SM-AHN)	Variable survival
Aggressive Systemic Mastocytosis (ASM)	
Median: ~2–4 years depending on mutation load & cytoreduction response	
Mast Cell Leukemia (MCL)	Poor prognosis
Median survival: <12 months despite therapy	

Monitoring Strategy

- Baseline and serial tryptase levels (proxy for MC burden)
- Organ involvement: liver function, spleen size, GI lesions
- Bone marrow: cellularity, MC aggregates, fibrosis

- Molecular markers:

✓KIT D816V allele burden

✓Additional mutations (e.g., SRSF2, ASXL1 → high-risk features)

- **Progression Risk**

✓ISM → ASM → MCL:

✓Risk increases with age, KIT allele burden, and multilineage involvement

- **Essential Follow-Up**

✓Monitor molecular evolution (via digital PCR/NGS)

✓Early detection of transformation aids treatment timing

Case Study

- Age/Sex: 4-year-old male
- History: Persistent itchy rash since age 2
- No systemic symptoms (no flushing, syncope, GI complaints)
- No prior anaphylaxis
- Clinical Findings
- Skin:

✓Multiple tan-brown maculopapular lesions

✓Positive Darier's Sign: local urticaria on rubbing

- Physical Exam:
- No hepatosplenomegaly
- No lymphadenopathy

- Labs:

✓Serum tryptase: 6.5 ng/mL (normal)

✓No KIT D816V mutation detected

✓Negative for CD2/CD25 expression on skin biopsy

Diagnosis

Maculopapular Cutaneous Mastocytosis (MPCM)

Management

- Topical corticosteroids for itch
- Daily non-sedating H1-antihistamines
- Parent education:
- Avoid triggers (heat, rubbing, NSAIDs)
- Epinephrine auto-injector prescribed as precaution

- **Follow-up**

✓Regular monitoring for signs of systemic involvement

✓Excellent prognosis – majority outgrow CM during adolescence

Take-Home Summary

- Mast Cell Disorders span from benign (CM) to fatal (MCL) phenotypes
- KIT D816V mutation is central in the pathogenesis of Systemic Mastocytosis (SM)
- Diagnosis = Tryptase + KIT mutation + CD2/CD25 expression
- Hereditary Alpha Tryptasemia (HaT) is under-recognized in allergy clinics
- Management is now precision-based

→ e.g., Midostaurin / Avapritinib for KIT-mutated AdvSM

Thank You

Mast cell disorders require a high index of suspicion, multidisciplinary input, and tailored management for optimal outcomes.