Systemic Mastocytosis (SM)
Diagnostic Checklist

Clinical Suspicion Cues

- ❍ Pigmented cutaneous lesions that urticate with pressure (Darier's sign positive)
- ❍ Anaphylaxis to insect venom
- ❍ History of anaphylaxis, especially if associated with baseline or event-related tryptase increases
- ❍ BST >8 ng/mL
- ❍ History of fractures (especially vertebral)
- ❍ History of hypotensive episodes resulting in presyncope or syncope + absence of urticaria and angioedema + elevated BST level
- ❍ History of flushing, itching, or hives
- ❍ History of unexplained abdominal pain or other GI symptoms
- ❍ History of fatigue, brain fog, or headaches
- ❍ Symptoms triggered by temperature changes, friction, stress, alcohol, or medications

	Recommended Tests	Abnormal Values That Increase Suspicion for SM
❍ **Bloodwork**	CBC/Diff	Cytopenias
	CMP	
	BST	>8 ng/mL
❍ **Genetics**	High-sensitivity *KIT* D816V mutation analysis on PB (ddPCR)	+
	Tryptase genotype (HαT)	
	Screen for *FIP1L1-PDGFRA* if eosinophilia is present and *KIT* D816V is negative	
	Myeloid NGS panel (optional)	
❍ **Morphology**	PB smear	
	BM aspirate smear	
	BM biopsy	Aggregates of ≥15 MCs
❍ **MC Immunophenotype**	Flow cytometry: CD2, CD25, CD34, CD117, CD30	Markers expressed on MCs
	Immunohistochemistry: tryptase, CD25, CD117, CD30	CD2/25/30 expression
❍ **Bone Health**	DEXA scan	

BM Biopsy if:

- ❍ PB *KIT* D816V^{+} (high-sensitivity assay)
- ❍ BST >20 ng/mL
- ❍ Clinical suspicion cues indicative of SM (eg, history of anaphylaxis, unexplained fractures, presyncope/syncope/MC mediator symptoms)

BM, bone marrow; BST, basal serum tryptase; CBC/Diff, complete blood count with differential; CMP, comprehensive metabolic panel; ddPCR, droplet digital PCR; DEXA, dual-energy X-ray absorptiometry; GI, gastrointestinal; HαT, hereditary alpha tryptasemia; MC, mast cell; NGS, next-generation sequencing; PB, peripheral blood; PCR, polymerase chain reaction.

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BETWEEN TREATMENT CENTERS & COMMUNITY PRACTICES: REDUCING KNOWLEDGE GAPS IN MANAGEMENT OF SYSTEMIC MASTOCYTOSIS

WHO 2022 SM Diagnostic Criteria

MAJOR CRITERIA	MINOR CRITERIA
○ Multifocal dense infiltrates of MCs (≥15 MC in aggregates) detected in BM and/or ECO(s).	○ >25% of all MCs with atypical MC morphology on BM smears or in other ECO(s)
1 major criterion + 1 minor criterion OR ≥3 minor criteria	○ *KIT* D816V or other activating *KIT* mutation detected
	○ Baseline serum tryptase >20 ng/mL; in the case of known HαT, adjust tryptase level
	○ CD2, CD25, and/or CD30 on MCs

In the case of HαT, the expected level of tryptase should be adjusted via

BST

1 + extra copy numbers of *TPSAB1*

For example, in a patient with BST = 18 ng/mL, but genetic testing reveals 2 extra copies of *TPSAB1*, the adjusted tryptase would be 6 ng/mL (normal).

SM Criteria Met (BM Evaluation + Clinical Findings)

- **Bone Marrow Mastocytosis (BMM)** ← **No additional findings**
  - Absence of skin lesions
  - BM involvement
  - Serum tryptase <125 ng/mL
- **Indolent SM (ISM)** ← **<2 B-findings**
  - Skin lesions may be present
- **Smoldering SM (SSM)** ← **≥2 B-findings, No C-findings**
- **Aggressive SM (ASM)** ← **≥1 C-finding**

+

- **≥20% MCs on BM aspirate smear** → **MCL[a]**
  - Classic MCL: ≥10% MCs in PB smear
  - Aleukemic MCL: <10% MCs in PB smear
- **WHO criteria for AHN met (eg, dysplasia, monocytosis, eosinophilia)** → **SM-AHN[a]**
  - SM-AML
  - SM-MDS
  - SM-MPN
  - SM-MDS/MPN (eg, SM-CMML)

B-findings

- ○ ≥30% MCs on BM biopsy and/or BST ≥200 ng/mL and/or *KIT* D816V VAF ≥10%
- ○ Signs of myeloproliferation and/or myelodysplasia not fulfilling criteria for an AHN
- ○ Hepatomegaly without impaired liver function and/or palpable splenomegaly without hypersplenism and/or lymphadenopathy (palpation or imaging)

C-findings

- ○ Cytopenia(s) present (ANC <1.0 × 10^9/L, Hgb <10 g/dL, or platelets <100 × 10^9/L)
- ○ Hepatomegaly with portal hypertension/ascites
- ○ Splenomegaly with hypersplenism
- ○ Osteolytic lesions (≥2 cm) or pathologic fractures
- ○ Malabsorption with weight loss with hypoalbuminemia

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AHN, associated hematologic neoplasm; AML, acute myeloid leukemia; ANC, absolute neutrophil count; CMML, chronic myelomonocytic leukemia; ECO, extracutaneous organ; Hgb, hemoglobin; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; VAF, variant allele frequency; WHO, World Health Organization.

[a]B- and C-findings possible; in acute MCL, C-findings are detectable.

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