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 eventrelated 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 <i>KIT</i> 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
O Bone Health	DEXA scan	

BM Biopsy if:

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



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	O KIT D816V or other activating KIT mutation detected
OR ≥3 minor criteria	O Baseline serum tryptase >20 ng/mL; in the case of known HαT, adjust tryptase level
	CD2, CD25, and/or CD30 on MCs

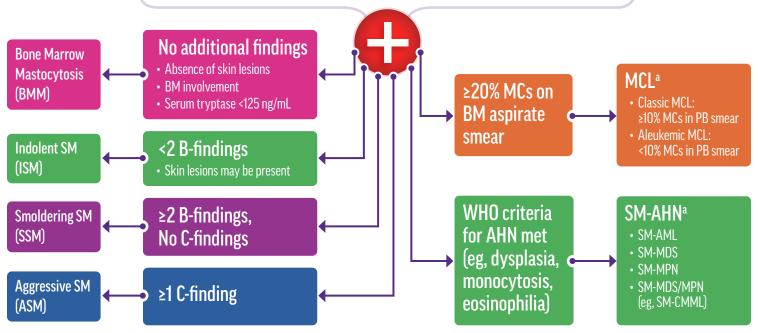
In the case of H α T, the expected level of tryptase should be adjusted via

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)



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

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





