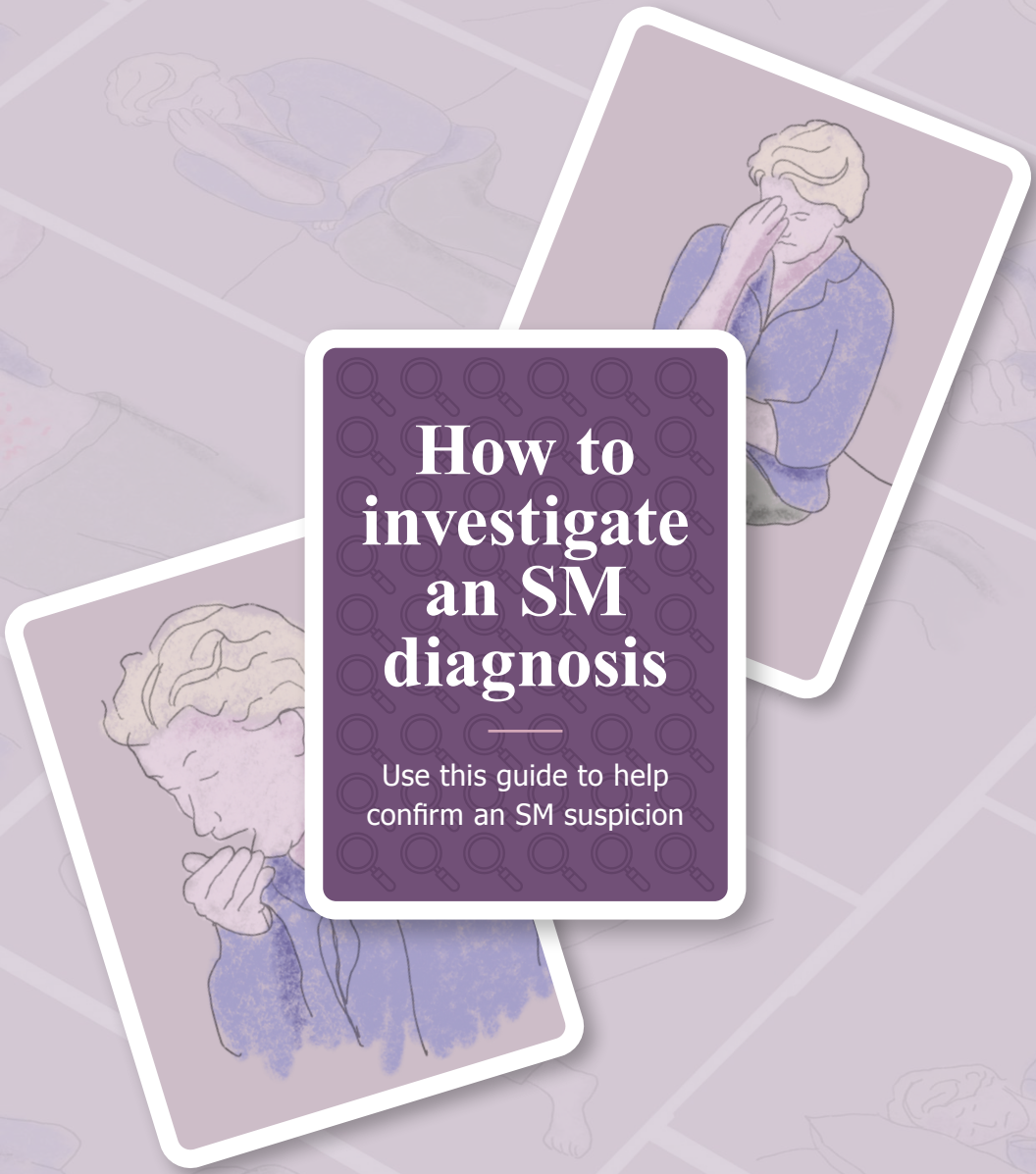

How to investigate an SM diagnosis

Use this guide to help confirm an SM suspicion

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A simplified diagnostic algorithm for adults with suspected systemic mastocytosis (SM)

This simplified diagnostic algorithm is based on the ECNM User's Guide (Valent 2022 *et al.*)[1] and other supporting published expert opinion (Theoharides *et al.*)[2] and is not intended to be a diagnostic tool. It does not replace the need for a complete evaluation of the patient by a healthcare professional.

Common symptoms that may trigger suspicion of SM include characteristic skin lesions, unexplained osteoporosis, anaphylaxis, histamine-induced symptoms (cramping, headache, hypotension, diarrhoea), cytopenia, eosinophilia and splenomegaly[1]

Serum tryptase testing should be performed upon clinical suspicion of SM[1,2]*

Serum tryptase <11.5 ng/mL[2]
Mastocytosis unlikely – but cannot be ruled out[1,2]

Follow up or monitor for increasing tryptase levels or clinical symptoms suggestive of SM[1,4]

Serum tryptase 11.5–20 ng/mL[2]
SM possible – screen for *KIT* D816V peripheral blood with high-sensitivity assay[1,2]

Serum tryptase ≥20 ng/mL[2]
WHO minor criterion[3]
Conduct a bone marrow biopsy or screen for *KIT* D816V peripheral blood with high-sensitivity assay[1,2]

Screen for *KIT* D816V mutation with droplet digital polymerase chain reaction (ddPCR)[1,2]

A highly sensitive PCR assay (e.g. ddPCR with ~0.01% sensitivity) is recommended for screening *KIT* D816V in peripheral blood. Next-generation sequencing (NGS) assays have low sensitivity (~1–5%) and are not sufficient to detect *KIT* D816V mutation[5]

In a study of ISM patients (n=39):[6]

95%
detection of *KIT* D816V mutation with ddPCR assay

28%
detection of *KIT* D816V mutation with NGS assay

Further work-up involves assessing if the patient meets the WHO diagnostic criteria (see the inside pages for full WHO criteria)

*Serum tryptase should be measured when the patient is at baseline and not immediately after an anaphylactic or mast cell activation event.[4]

ECNM=European Competence Network on Mastocytosis; ISM=indolent systemic mastocytosis; WHO=World Health Organization.

WHO criteria are used to diagnose SM[3]

Diagnosis of SM requires 1 major and ≥1 minor criterion OR ≥3 minor criteria

Major criterion

Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates)
In bone marrow biopsies and/or in sections of other extracutaneous organ(s)

Minor criteria

≥25% of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in mast cell infiltrates
Detected in sections of bone marrow or other extracutaneous organs

Activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT*
In bone marrow or another extracutaneous organ

Mast cells in bone marrow, blood or another extracutaneous organ express one or more of: CD2 and/or CD25 and/or CD30

Baseline serum tryptase concentration >20 ng/mL (in the absence of an unrelated myeloid neoplasm)
In the case of a known HαT, the tryptase level should be adjusted

HαT=hereditary alpha-tryptasemia; WHO=World Health Organization.

WHO B- and C-findings are used to determine the subtype of SM[3]

C-findings

- **Cytopenia/s:** ANC <1×10^9/L, Hb <10 g/dL, PLT <100×10^9/L (one or more found)
- **Hepatopathy:** Ascites and elevated liver enzymes ± hepatomegaly or cirrhotic liver ± portal hypertension
- **Spleen:** Palpable splenomegaly with hypersplenism ± weight loss ± hypoalbuminemia
- **Gastrointestinal tract:** Malabsorption with hypoalbuminemia ± weight loss
- **Bone:** Large-sized osteolysis (≥2 cm) with pathologic fracture ± bone pain

B-findings

- **High mast cell burden:** Infiltration grade (mast cells) in bone marrow ≥30% in histology (IHC) and/or serum tryptase ≥200 ng/mL and/or *KIT* D816V VAF ≥10% in bone marrow or peripheral blood leukocytes
- **Signs of myeloproliferation and/or myelodysplasia:** Hypercellular bone marrow with loss of fat cells and prominent myelopoiesis ± left shift and eosinophilia ± leukocytosis and eosinophilia and/or discrete signs of myelodysplasia (<10% neutrophils, erythrocytes and megakaryocytes)
- **Organomegaly:** Palpable hepatomegaly without ascites or other signs of organ damage or/and palpable splenomegaly without hypersplenism and without weight loss or/and lymphadenopathy palpable or visceral LN-enlargement found in ULS or CT (>2 cm)

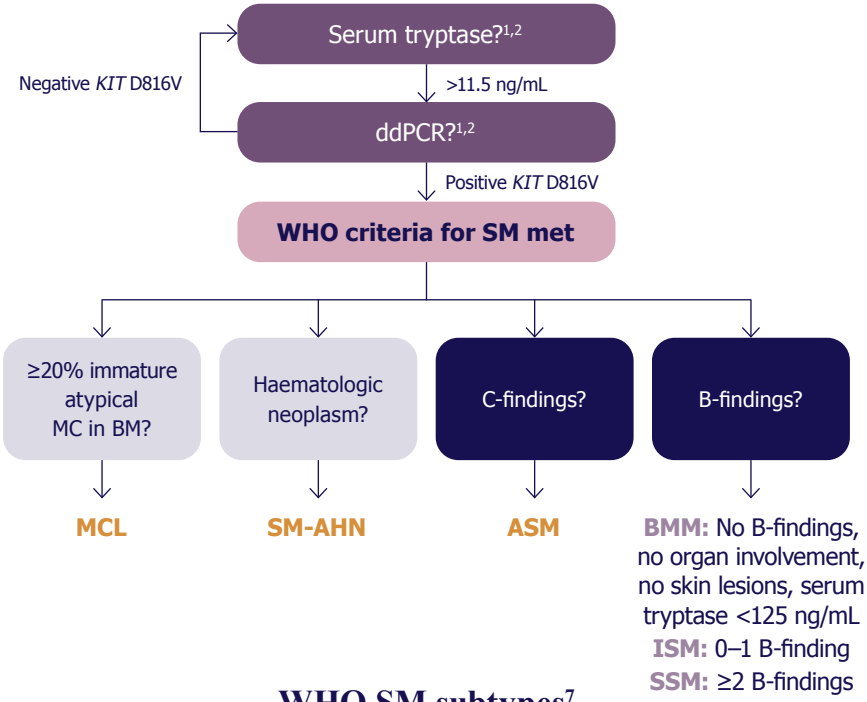
*Signs of myeloproliferation and/or myelodysplasia must be discrete and stable (neither disappear nor progress) and must not reach diagnostic criteria of an MPN, MDS or MPN/MDS, in which case the diagnosis changes to SM-AHN. The presence of a myeloid AHN excludes B-findings and SSM by definition.

**Alkaline phosphatase levels are typically elevated in patients with Advanced SM and SM-induced liver damage. In some of these patients, only elevated liver enzymes but no (clinically relevant) ascites are found.

AHN=associated hematologic neoplasm; ANC=absolute neutrophil count; CT=computed tomography; Hb=haemoglobin; IHC=immunohistochemistry; LN=lymph node; MDS=myelodysplastic syndrome; MPN=myeloproliferative neoplasm; PLT=platelet count; SSM=smouldering systemic mastocytosis; ULS=ultrasound; VAF=variant allele frequency; WHO=World Health Organization.

Diagnosing SM: An overview[3,7]

This simplified diagnostic algorithm is based on the WHO criteria[3,7]



WHO SM subtypes[7]

Advanced SM	Non-Advanced SM
Mast cell leukaemia (MCL)	Bone marrow mastocytosis (BMM)
Systemic mastocytosis with an associated haematological neoplasm (SM-AHN)	Smouldering systemic mastocytosis (SSM)
Aggressive systemic mastocytosis (ASM)	Indolent systemic mastocytosis (ISM)

BM=bone marrow; ddPCR=droplet digital polymerase chain reaction; MC=mast cell; WHO=World Health Organization.

References: 1. Valent P, *et al. J Allergy Clin Immunol Pract.* 2022;10(8):1999–2012.e6. **2.** Theoharides TC, *et al. N Engl J Med.* 2015;373(2):163–172. **3.** Valent P, *et al. Hemasphere.* 2021;5(11):e646. **4.** Akin C. *Hematology Am Soc Hematol Educ Program.* 2022;2022(1):55–63. **5.** Hoermann G, *et al. J Allergy Clin Immunol Pract.* 2022;10(8): 1953–1963. **6.** George TI, *et al. Blood.* 2020;136(Suppl 1):7. **7.** Khoury JD, *et al. Leukemia.* 2022;36(7):1703–1719.