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Multidisciplinary insights: Navigating the challenges of systemic mastocytosis diagnosis and management

Practice aid for systemic mastocytosis

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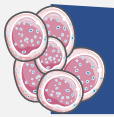
Spectrum of symptoms in patients with systemic mastocytosis



Clinical spectrum of disease burden and aggressiveness[1]

Pre-diagnostic	ISM	SSM	ASM SM-AHN	MCL

MC mediator/skin symptoms prominent → **Organopathy prominent**

Skin[1]

- Urticaria
- Flushing
- Pruritus

GI[1]

- Abdominal cramps
- Diarrhoea
- Heartburn
- Nausea
- Vomiting

Neurological[1,2]

- Cognitive/memory difficulties
- Depression
- Headache

Bone[1]

- Back pain
- Bone pain
- Osteoporosis

Anaphylaxis[1]

- Dizziness
- Palpitations
- Syncope

Constitutional[1]

- Arthralgias
- Chills
- Fatigue
- Myalgias
- Sweats
- Weakness

Ensure organopathy is due to MC infiltration[1]

- Ascites/hepatomegaly
- Cytopenias
- Hypersplenism/splenomegaly
- Lymphadenopathy
- Malabsorption or protein-losing enteropathy + weight loss
- Osteolysis + pathologic fractures

Diagnostic work-up for systemic mastocytosis: ICC and WHO criteria

Diagnostic algorithm[1]

- **Serum tryptase level**
- **BM, blood or other extracutaneous tissue:** MC expression of CD25 and/or CD30 and/or CD2 evaluated by FCM, IHC or both
- **Molecular testing:** Activating *KIT* mutation, including *KIT*^{D816V}
- **If eosinophilia present:** *FIP1L1-PDGFRA* screening

ICC[4]/WHO[5] SM criteria

ICC[3,4]

- **Presence of major criterion sufficient for diagnosis** or
- **≥3 minor criteria diagnostic** if major criterion absent

Major criterion

Multifocal dense infiltrates of tryptase and/or CD117+ MCs (≥15 MCs in aggregates)
detected in sections of BM/other extracutaneous organ(s)

Minor criteria

- >25% MCs are spindle-shaped or have an atypical immature morphology
- CD25, CD2 and/or CD30 MCs expressed in addition to MC markers†
- *KIT*^{D816V} mutation or activating KIT mutation†
- ↑ serum tryptase, persistently >20 ng/mL
  In SM-AMN ↑ tryptase is not an SM minor criterion (see next slide)

WHO[3,5]

- **Presence of ≥1 major criterion and 1 minor criteria,** or
- **3 minor criteria required for diagnosis**

Major criterion

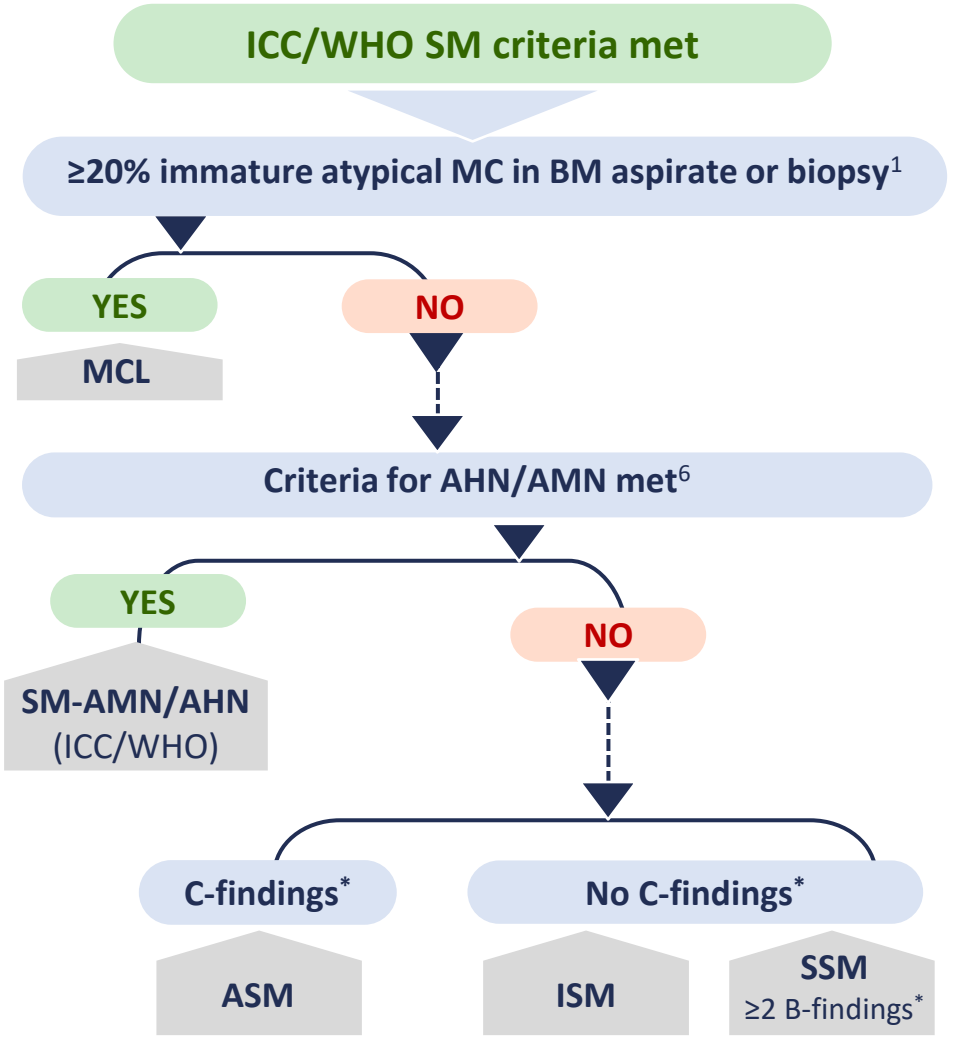
Multifocal dense infiltrates of MCs (≥15 MCs in aggregates)
detected in BM biopsies/sections of other extracutaneous organ(s)

Minor criteria

- >25% MCs are atypical (type I/II) on BM smears, or spindle-shaped in MC infiltrates on visceral organs
- MCs exhibit CD2 and/or CD25†
- *KIT*^{D816V} mutation or activating KIT mutation†
- Baseline serum tryptase >20 ng/mL
  In unrelated myeloid neoplasm tryptase is not an SM criterion

†Detected in BM, peripheral blood, or another extracutaneous organ.

Diagnostic work-up for systemic mastocytosis: 2022 updates to subtype classification



***Diagnosis of SM variants requires correlation with B- and C- findings[4–6]**

- B-findings represent burden of disease
- C-findings represent SM-induced organ damage

Refined diagnostic criteria for SM-AMN/-AHN[6]

ICC

SM-AMN†

Meets:

- **SM diagnostic criteria**
- **The criteria for an associated MN**
  e.g. CMML or other MDS/MPN, MDS, MPN, AML or other MN
- *The associated MN should be fully classified according to established criteria*

WHO

SM-AHN

Meets:

- **SM diagnostic criteria**
- **WHO criteria for myeloid AHN type or lymphoid AHN type**

†*SM-AHN is modified to SM-AMN in the new ICC criteria, as SM-AHN is limited to the presence of an associated MN, with which it often also shares* KIT *mutations and/or clonal genetic abnormalities*

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Management options for systemic mastocytosis

Tailor to the individual patient's disease subtype, symptoms, and overall health status[3,7]

Non-advanced[3]

ISM / SSM

Carry adrenaline autoinjector
Assess symptom burden-PROs
Consider known triggers
Assess MC-related comorbidities:
DEXA scan at diagnosis, then surveillance

Is the patient symptomatic?

NO

Annual review
- Symptom assessment
- Blood counts
- Clinical evaluation

YES

Symptomatic therapy
- Anti-H1/-H2 antihistamines; MC stabilizers
- Immunotherapy (e.g. omalizumab) may be considered in patients with IgE-mediated allergic reactions[1]
- Venom immunotherapy[8]
- Avapritinib for moderate-to-severe ISM[9,10]
- Consider analgesia/bisphosphonates/ psychotherapy

Advanced[7]

ASM / SM-AHN* / MCL

Carry adrenaline autoinjector/anti-mediator medications

Which component needs treatment?

SM
- Avapritinib *(platelets >50x10^9/L)* OR
- Midostaurin
- Imatinib for patients with *KIT*^{D816V}-negative/WDSM
- Cladribine
- Consider allogeneic-HSCT

AMN/AHN
- Appropriate AHN-directed treatment
- Consider SM-directed treatment if persistent
- Sequential/ combination treatment
- Consider allogeneic-HSCT

MCL
- Avapritinib (platelets >50x10^9/L) OR
- Midostaurin
- Cladribine
- Combination chemotherapy
- Consider allogeneic-HSCT

Consider clinical trial

*Definitions: AMN (ICC) and AHN (WHO).

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Abbreviations and references

Abbreviations

AHN, associated haematological neoplasm; AML, acute myeloid leukaemia; AMN, associated myeloid neoplasm; ASM, aggressive SM; BM, bone marrow; CMML, chronic myelomonocytic leukaemia; DEXA, dual energy x-ray absorptiometry; FCM, flow cytometry; GI, gastrointestinal; H, histamine; HSCT, haematopoietic stem cell transplant; ICC, International Consensus Classification; IgE, immunoglobulin E; IHC, immunohistochemistry; ISM, indolent SM; MC, mast cell; MCL, mast cell leukaemia; MDS, myelodysplastic syndrome; MN, myeloid neoplasm; MPN, myeloproliferative neoplasm; PRO, patient-reported outcome; SM, systemic mastocytosis; SSM, smoldering SM; WDSM, well-differentiated SM; WHO, World Health Organization.

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