

A large, stylized orange grid pattern resembling a globe or a network, composed of thick, curved lines that intersect to form a grid of irregular shapes. The pattern is centered and occupies most of the page.

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

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**Practice aid for systemic mastocytosis**

For more information, visit: [www.touchhaematology.com](http://www.touchhaematology.com)

## Spectrum of symptoms in patients with systemic mastocytosis



Clinical spectrum of disease burden and aggressiveness<sup>1</sup>



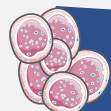
Pre-diagnostic

ISM

SSM

ASM  
SM-AHN

MCL



MC mediator/skin symptoms prominent

Organopathy prominent



Skin<sup>1</sup>

- Urticaria
- Flushing
- Pruritus



Bone<sup>1</sup>

- Back pain
- Bone pain
- Osteoporosis



GI<sup>1</sup>

- Abdominal cramps
- Diarrhoea
- Heartburn
- Nausea
- Vomiting



Anaphylaxis<sup>1</sup>

- Dizziness
- Palpitations
- Syncope



Neurological<sup>1,2</sup>

- Cognitive/memory difficulties
- Depression
- Headache



Constitutional<sup>1</sup>

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

Ensure organopathy is due to MC infiltration<sup>1</sup>

- 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<sup>1</sup>

- 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*<sup>D816V</sup>
- **If eosinophilia present:** *FIP1L1-PDGFR*A screening

### ICC<sup>3,4</sup>

- 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<sup>†</sup>
- *KIT*<sup>D816V</sup> mutation or activating *KIT* mutation<sup>†</sup>
- ↑ serum tryptase, persistently >20 ng/mL  
*In SM-AMN ↑ tryptase is not an SM minor criterion (see next slide)*

### ICC<sup>4</sup>/WHO<sup>5</sup> SM criteria

### WHO<sup>3,5</sup>

- 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<sup>†</sup>
- *KIT*<sup>D816V</sup> mutation or activating *KIT* mutation<sup>†</sup>
- Baseline serum tryptase >20 ng/mL  
*In unrelated myeloid neoplasm tryptase is not an SM criterion*

<sup>†</sup>Detected in BM, peripheral blood, or another extracutaneous organ.

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

## ICC/WHO SM criteria met

≥20% immature atypical MC in BM aspirate or biopsy<sup>1</sup>

YES

MCL

NO

Criteria for AHN/AMN met<sup>6</sup>

YES

SM-AMN/AHN  
(ICC/WHO)

NO

C-findings\*

ASM

No C-findings\*

ISM

SSM

≥2 B-findings\*

\*Diagnosis of SM variants requires correlation with B- and C- findings<sup>4-6</sup>

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

## Refined diagnostic criteria for SM-AMN/-AHN<sup>6</sup>

### ICC

#### SM-AMN<sup>†</sup>

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

<sup>†</sup>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

# Management options for systemic mastocytosis

Tailor to the individual patient's disease subtype, symptoms, and overall health status<sup>3,7</sup>

## Non-advanced<sup>3</sup>

### ISM

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

### SSM

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<sup>1</sup>
- Venom immunotherapy<sup>8</sup>
- Avapritinib for moderate-to-severe ISM<sup>9,10</sup>
- Consider analgesia/bisphosphonates/psychotherapy

## Advanced<sup>7</sup>

### ASM

### SM-AHN\*

### MCL

Carry adrenaline autoinjector/anti-mediator medications

Which component needs treatment?

SM

AMN/AHN

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

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

- Avapritinib (*platelets* >50x10<sup>9</sup>/L)  
OR
- Midostaurin
- Cladribine
- Combination chemotherapy
- Consider allogeneic-HSCT

Consider clinical trial

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

# 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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