Classification, Diagnosis, and Management of Systemic Mastocytosis in 2019

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The Mast Cell

- Develop from CD34+ pluripotent progenitor cells
- Express Kit receptor for SCF = kit ligand
- Mature in the periphery under micro-environmental influence
- Interaction between KIT and SCF plays an essential role in mast cell development
- Activating somatic mutations in c-kit in patients with mastocytosis
**Kit Structure**

![Diagram of Kit structure with modifications](image)

- **Modification option 2**: Ig-like domains
- **V560G**
- **D816V**
- **D816I**
- **D816Y**
- **Ligand Binding**
- **Dimerization**
- **Transmembrane Domain**
- **Juxtamembrane Domain**
- **Cytoplasmic Tail**
- **Kinase Domain I**
- **Kinase Inset**
- **Kinase Domain II**

*Metcalfe and Mekori Ann Rev Pathol, 2017*
Mast Cell Activation as a Prediagnostic Checkpoint

Typical clinical symptoms + transient increase in serum tryptase levels or transient increase of another established MC mediator + response to anti-mediator drugs

MCA

Monoclonal MCs (KIT D816V or other KIT exon 17 mutations)

Primary MCAS

3 minor or 1 major + 1 minor SM criteria

SM$_{SY}$

CM$_{SY}$

Secondary MCAS

1 or 2 minor and no major SM criteria

MIS criteria

No MIS

(Mono)clonal MCAS

Idiopathic MCAS

Type I allergy of another underlying disease leading to MCA

No allergy, no other underlying disease, no monoclonal MCs and no MIS detected
How we diagnose and treat systemic mastocytosis in adults
Presentation of Mastocytosis

- Urticaria Pigmentosa 70%
- Anaphylaxis 20% *
- Fractures 10%

* mosquito, hymenoptera, radiocontrast etc.

Signs and Symptoms related to:
MC activation and mediator release
MC infiltration and tissue damage
Symptoms of Mastocytosis

1. Constitutional – fatigue, weight loss, fever, diaphoresis
2. Skin - pruritus, urticaria, dermatographism, flushing
3. Mediator-related systemic events - abdominal pain, gastrointestinal distress, syncope, headache, hypotension, tachycardia, respiratory symptoms
4. Musculoskeletal complaints - bone pain, osteopenia/osteoporosis, fractures, arthralgias, myalgia

➢ Organ impairment (due to mast cell infiltrates) – advanced disease*
WHO Diagnostic Criteria for Systemic Mastocytosis*

**Major criterion**
- Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) in marrow or other extracutaneous organs

**Minor criteria**
- >25% of mast cells with spindled/atypical morphology
- *KIT* point mutation at codon 816 (*KIT* D816V)
- CD2 or CD25 expression in mast cells
- Serum total tryptase > 20 ng/ml, unless there is an associated clonal myeloid disorder

* Diagnosis of SM requires 1 major + 1 minor, or 3 minor criteria for this diagnosis
2016 WHO Classification of Mastocytosis

Cutaneous mastocytosis (CM; confined to the skin)

Systemic mastocytosis (SM)
- Indolent SM (ISM)
- Smoldering SM (SSM)
- SM with Associated Hematologic Neoplasms (SM-AHN)
  - Aggressive SM (ASM)
  - Mast cell leukemia (MCL)

Mast cell sarcoma (MCS)

Cancer Res, 2017
Indolent SM

Smoldering SM
(SM in transition)

Advanced SM
(ASM, MCL, SM-AHN) with organ damage

2 or more “B Findings”

1. Bone marrow biopsy: >30% mast cells and serum tryptase level >200 ng/ml
2. Signs of dysplasia or myeloproliferation, without signs of frank AHN, and normal or mildly abnormal blood counts
3. Hepatomegaly without liver dysfunction, and/or palpable splenomegaly without hypersplenism, lymphadenopathy

“C Findings” (Organ Damage)

1. One or more cytopenias (ANC < 1x10^9/L, or Hb < 10 g/dL, or platelets < 100x10^9/L)
2. Palpable hepatomegaly with liver dysfunction, ascites, and/or portal hypertension
3. Osteolytic bone lesions and/or fractures
4. Palpable splenomegaly with hypersplenism
5. Malabsorption (hypoalbuminemia) with weight loss due to GI mast cell infiltrates
Diagnostic algorithm for systemic mastocytosis

- Serum tryptase level
- Bone marrow biopsy:
  - Tryptase and CD25 immunohistochemistry
  - Flow cytometry for MC CD25 expression if IHC indeterminate
- Molecular testing for KITD816V mutation (bone marrow, blood or other lesional specimen)
- FIP1L1-PDGFRα screening if eosinophilia present – bone marrow or blood

WHO criteria for SM met

WHO criteria for associated hematological neoplasm satisfied?

- YES
  - ≥20% MC on BM aspirate smear
  - SM-AHN

- NO
  - 10% in PB
  - MCL
  - C-findings
  - ASM
  - No C-findings
  - ISM (SSM: ≥2 B-findings)

Pardanani AJH 2019
Diagnostic evaluation of the AHN

**SM +**

- **MDS**
  - Cytogenetics; mutation studies

- **MDS/MPN** (e.g. CMML)
  - Cytogenetics; mutation studies

- **MPN** (CML, PMF)
  - **BCR-ABL, JAK2 V617F**

- **HES/CEL**
  - **PDGFRA/B, cytogenetics**

- **AML**
  - Cytogenetics (e.g. t(8;21)), **FLT3 / NPM1, ASXL 1**

- **Myeloma**
  - Cytogenetics, FISH panel

- **Lymphoma**
  - Subtype-directed evaluation
## Survival for SM Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>% of SM</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM-AHNMD</td>
<td>(n=138)</td>
<td>40</td>
</tr>
<tr>
<td>ASM</td>
<td>(n=41)</td>
<td>12</td>
</tr>
<tr>
<td>MCL</td>
<td>(n=4)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Lim K.-H et al.** *Blood*. 2009

[Graph showing survival rates for different subtypes of SM.]
Rare Imatinib sensitive

Imatinib resistant

Point mutation D816V (Y,F,H) D820G

D816V~90%

Juxtamembrane domain
Kinase 1 domain
Kinase insert domain
C-terminus

Immunoglobulin-like loops

Point mutation F522C V530I

Transmembrane domain
Extracellular

Cell membrane

KIT Mutations: Implications for TK Inhibitors
IF positive in the BM, KIT D816V was found in PB of all patients with advanced SM (SM-AHNMD, ASM, MCL) and in 46% of patients with ISM

Strong correlation of allele burden (of D816V) with disease activity (tryptase), disease subtype (indolent Vs advanced) and survival
SM Genetics: Beyond $KIT$ D816V

$KIT$ D816V positive (n = 12)

$KIT$ D816V positive plus at least one additional mutation (n = 26)

$P = .019$

Schwaab et al, Blood, 2013
Prognostic Scoring of Mastocytosis with the Inclusion of Next Generation Sequencing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score allotment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count &lt; 150 × 10^9/l</td>
<td>2 points</td>
</tr>
<tr>
<td>Serum albumin &lt; 35 g/l</td>
<td>1.5 points</td>
</tr>
<tr>
<td>Haemoglobin &lt; 100 g/l or red blood cell transfusiondependence</td>
<td>1 point</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>1.5 points</td>
</tr>
<tr>
<td>ASXL1 mutation</td>
<td>1.5 points</td>
</tr>
<tr>
<td>Risk Score (cumulative points)</td>
<td>Median survival</td>
</tr>
<tr>
<td>Low risk (0–1.5)</td>
<td>86 months</td>
</tr>
<tr>
<td>Intermediate risk (2–4.5)</td>
<td>21 months</td>
</tr>
<tr>
<td>High risk (5–7.5)</td>
<td>5 months</td>
</tr>
</tbody>
</table>

Pardanani et al AJH, 2016
Survival curves for 106 patients with advanced systemic mastocytosis stratified by number of mutations in non-KIT genes.

Mutation-Augmented Prognostic Scoring System (MAPSS)

Pardanani A et al. AJH 2016
Additional Diagnostic Testing in SM

- **GI symptoms (diarrhea, ulcers, bleeding)**
  - Endoscopy/colonoscopy with biopsies for MC with IHC stains

- **Organomegaly / Organopathy**
  - Ultrasound / CT (3D) for hepatosplenomegaly, ascites, lymph nodes
  - Liver biopsy

- **Bones**
  - Skeletal survey to evaluate for sclerotic and lytic lesions
  - DEXA scan : osteoporosis

- **Biochemical evidence of mast cell activation / mediator release**
  - Histamine level ; 24 hr urine N-methylhistamine, or prostaglandin D2 or metabolites
  - Heparin level if unusual bleeding or prolonged PTT
IHC and Flow Cytometry to Evaluate Mast Cell Burden

CD117 (~70%)  CD25 (~70%)  Tryptase (~50%)
Mast cell mediator / skin symptoms prominent

Skin: pruritus, flushing, hives
Gastrointestinal: nausea, vomiting, diarrhea, abdominal cramps, heartburn
Cardiovascular: syncope, dizziness, palpitations
Neurologic: memory/cognitive difficulties, depression, headache, sleep disturbance

Anaphylaxis
(hypotension >> angioedema)
Hymenoptera stings, drugs, food

Bone: osteopenia, osteoporosis, back pain, bone pain
Constitutional: generalized weakness, fatigue, arthralgias, myalgias, sweats, chills

Ensure that organopathy is due to mast cell infiltration!
- Osteolysis w/ pathologic fractures
- Lymphadenopathy
- Splenomegaly/hypersplenism
- Hepatomegaly/ascites
- Cytopenias
- Malabsorption or protein-losing enteropathy w/ weight loss

Organopathy prominent

Pre-diagnostic SM
Indolent SM
Smoldering SM?
Aggressive SM / SM + associated hematological malignancy
Mast cell leukemia

Disease burden / aggressiveness
Clonal Prediction Model in Idiopathic Anaphylaxis

<table>
<thead>
<tr>
<th>TABLE IV. Clonal mast cell predictability tables: Mast cell activation symptom scores (NICAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Clinical symptoms</td>
</tr>
<tr>
<td>Absence of angioedema</td>
</tr>
<tr>
<td>Flushing</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Tryptase</td>
</tr>
<tr>
<td>&lt;11.4 ng/mL</td>
</tr>
<tr>
<td>&gt;11.4 ng/mL</td>
</tr>
<tr>
<td>Allele-specific PCR</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
</tr>
</tbody>
</table>

A total score of 2 or greater is predictive of clonal disease.

NICAS, NIH Idiopathic Clonal Anaphylaxis Score.

> 3 anaphyl. events/year
15% clonal MC disease

Carter M et al JACI 2017
# Treatment of Systemic Mastocytosis

## Drugs for mediator symptoms/anaphylaxis
- H1/H2 Anti-histamines
- Leukotriene antagonists [montelukast]
- Mast cell stabilizers [cromolyn sodium; ketotifen]
- Bisphosphonates for osteoporosis; IV for osteolyses/factures
- Epipen; venom immunotherapy

**Avoidance of triggers**

## Cytoreductive therapy
- [PEG] Interferon-α
- 2-Chlorodeoxyadenosine
- Corticosteroids
- Multi-agent chemotherapy
- Transplantation

## Targeted therapy / trials
- Midostaurin
- Dasatinib / nilotinib
- Masitinib
- Imatinib
- Everolimus
- Daclizumab
- Omalizumab

*Pardanani A, Amer J Hematol 90:250, 2015*
Treatment algorithm for systemic mastocytosis (SM)

**Indolent SM**
- Avoid triggers of MC degranulation (aspirin, narcotics, alcohol, venoms, anesthetics)
- Symptoms of MC degranulation?
  - H1 and H2 blockers
  - Cromolyn sodium
  - Epi-Pen
  - MC cytoreductive agents (rarely)

**Aggressive SM (MC cytoreductive therapy)**
- Interferon-α ± Prednisone (1-5 million units IM)
- OR
- 2-Chloro-2-deoxyadenosine (5 mg/m²/day x 5 days q4-6 weeks)
- No response
- Investigational agent

**SM with associated hematological neoplasm**
- Treatment directed towards the associated neoplasm
- Imatinib 100 mg/day

**Investigational agent**
- Novel agent (clinical trial)
- Imatinib 400-600 mg/day (KITD816V negative cases)
- Dasatinib 70-140 mg/day
- Midostaurin (PKC412)
Hypothesis

The alternative small molecule tyrosine kinase inhibitor midostaurin (PKC412) can inhibit the imatinib-resistant KIT D816V mutation in systemic mastocytosis
Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis

Volume 374(26):2530-2541
June 30, 2016

- Midostaurin is a multikinase inhibitor that includes mutant and nonmutant KIT D816V as a target.
- Its use in patients with advanced systemic mastocytosis, including mast-cell leukemia, produced overall responses in 60%, with a median overall survival of 28.7 months.
- Median overall survival in MCL was 9.4 months
Decreased Frequency of MSAS Symptoms

Gotlib Ann Oncol
2017

Baseline MSAS (n = 37)

Best TMSAS value on treatment (n = 37)
Decreased Frequency of MSAS Symptoms

Baseline MSAS (n = 37)
Best TMSAS value on treatment (n = 37)
OS depending on the presence and dynamic of molecular parameters on midostaurin

OS depending on mutational status in the SRSF1/ASXL1/RUNX1 gene panel

OS depending on the expressed KIT D816V allele burden

Jawhar M Blood, 2017
SM - Prognostication

Advanced SM = 2
Age > 60 = 1
Platelets<150 = 1
Alk phos = 1
Mutations = 1

Pardanani Blood Adv 2018
Figure 4. Treatment flow chart for advanced systemic mastocytosis

Systemic mastocytosis

C findings? AHN? >20% mast cells on BM smear?

YES

ISM and SSM

NO

ASM
MCL

Midostaurin
Cladribine
Interferon
Polychemotherapy

Treatment for AHN

ACST according to age, comorbidities, type of AHN, prognosis factor

Treatment for AdvSM

ISM = allogeneic stem cell transplantation, AdvSM = advanced systemic mastocytosis, AHN = associated hematologic neoplasm, ASM = aggressive systemic mastocytosis, BM = bone marrow, MCL = mast cell leukemia, SM-AHN = systemic mastocytosis with an associated hematologic neoplasm

Rossignol J et al. F1000, 2019
Fig 4. Suggested initial treatment algorithm of systemic mastocytosis (SM) by subtype.

**Diagnosis of SM**

- **Cutaneous, Indolent or Systemic SM without progression**
  - Bone density management
  - Continued symptom management
  - Monitoring for progressive disease

- **Rapidly Progressing Systemic SM or Aggressive SM**
  - Bone density management
  - Continued symptom management
  - If KIT positive, midostaurin
  - If KIT negative, dasatinib or imatinib
  - Hydroxycarbamide can be considered if cytoreduction is needed
  - Interferon
  - Consider testing for CD30 overexpression. If positive, consider brentuximab
  - Clinical Trial

- **Mast Cell Leukaemia**
  - Midostaurin
  - High-dose cytosine arabinoside and a nucleoside such as fludarabine or cladribine
  - Stem cell transplant if candidate
  - Consideration of clinical trial
Avapritinib potently and selectively targets \textit{KIT} D816V

\begin{table}
\begin{tabular}{|l|l|l|l|l|l|}
\hline
 & \textit{KIT} D816V biochemical IC$_{50}$ \\
\hline
avapritinib* & imatinib* & masitinib$\#$ & midostaurin* & ripretinib$\#$ \\
0.27 nM & 8150 nM & >1000 nM & 2.9 nM & 2.6 nM \\
\hline
\end{tabular}
\end{table}

Biochemical binding by DiscoverRX at 3\mu M

\textsuperscript{*}Evans EK et al. Sci Transl Med. 2017;9(414)

\textsuperscript{#}Blueprint Medicines internal data on file

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Cooperation with Foreign Institutions

- Koln – Germany
- Toledo – Spain
- NIH – Bethesda, MD, USA
- Stanford, USA
- UNSW – Sydney, Australia

International Organizations

- European mast cell network (EMBRN)
- European competence network on mastocytosis (ECNM)