Signs & Symptoms

Activated mast cells release granules containing proinflammatory mediators and can result in:

- Maculopapular lesions with Darier's sign
- Recurrent or unexplained anaphylaxis often coupled with hypotension and syncope
- Recurring and unexplained gastrointestinal upset (i.e., recurring and unexplained nausea, vomiting, and/or diarrhea)
- Persistently elevated baseline serum tryptase levels; serum tryptase levels that increase by 20% above the baseline level plus an additional 2 ng/mL if measured within 4 hours after the onset of the acute event
- Unexplained osteoporosis (particularly in males)
- Unexplained hepatopathy with ascites
- Presence of adult onset cutaneous mastocytosis
- Chronic use of prescription medications for the treatment of unexplained allergies (e.g., corticosteroids, mast cell stabilizers)

Diagnostics & Testing

Proceed to a diagnostic workup if SM is suspected with symptoms consistent with mast cell disorder and no known cause:

- A diagnostic workup consisting of a history and physical including metabolic panel, CBC with differential, and blood smear examination
- Test for serum tryptase levels

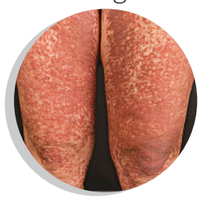
- Molecular testing for **KIT D816V: NCCN Guidelines recommends using a highly sensitive assay such as ASO-qPCR or digital droplet PCR on peripheral blood for initial screening**; A thorough analysis of KIT mutational status should include **bone marrow evaluation**

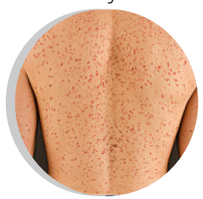
- Bone marrow aspirate and biopsy with flow cytometry (CD34, CD117, CD25, CD30, CD2), IHC (CD117, CD25, CD30, tryptase), cytogenetics
- FISH as needed for associated hematologic neoplasm (AHN)-related abnormalities

- Test for additional genomic mutations via NGS, especially in advanced SM
- Evaluation of B- and C- findings and organ involvement

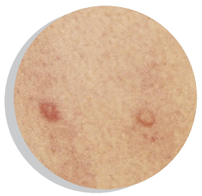
Lesions

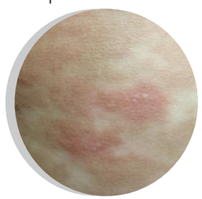
Small monomorphic lesions appear on the thighs or trunk of the body





Wheal-and-flare reaction is elicited by stroking lesion with a tongue spatula





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Did You Know?

Systemic mastocytosis (SM) is a rare, clonal mast cell neoplasm most commonly driven by the KIT D816V mutation[1,2]

Patients experience significant symptom burden with poor quality of life that can result in a reduced ability to work, higher rates of health care visits, polypharmacy, and severe pain[3]

Commercial Laboratories Offering NCCN Recommended High-Sensitivity KIT D816V Assays

Laboratory	Test Code/Name	Website	Phone
ARUP Laboratories[4]	3002956	www.aruplab.com	1-800-522-2787
Mayo Clinic Laboratories[5]	KITVS	www.mayocliniclabs.com	1-800-533-1710
Virant Diagnostics[6]	High Sensitivity cKIT D816V Mutation Hotspot	www.virantdx.com	1-877-888-2973
Labcorp[7]	485126	www.oncology.labcorp.com	1-877-442-3226
Blueprint-sponsored Biomarker Testing Program[8]	485140	www.oncology.labcorp.com/blueprintsm KIT D816V testing available at no charge for patients who are being evaluated for systemic mastocytosis. Program eligibility criteria apply	

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7. KIT (D816V) digital PCR. Labcorp. Accessed May 2023. https://www.labcorp.com/tests/485126/kit-d816v-digital-pcr
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Diagnostics Criteria

Diagnosis of SM requires the major criterion alone (ICC)[10] or with 1 minor criteria (WHO)[12] OR ≥3 minor criteria (ICC and WHO)[10, 12, 13]:

Major Criterion:
Multifocal dense infiltrates of MCs (≥15 mast cells in aggregates) detected in sections of bone marrow and/or sections of other extracutaneous organ(s) such as the GI tract

Minor Criterion:

- **More than 25% of MCs** in bone marrow (biopsy section or aspirate smears) or other extracutaneous organ(s) show **abnormal morphology** (i.e., atypical MC type 1 or are spindle-shaped MCs) in multifocal lesions in histologic examination
- **KIT D816V mutation** or other activating KIT mutation in extracutaneous organ(s) (in most cases bone marrow) or peripheral blood
- KIT+ MCs in bone marrow show **abnormal expression of CD2, CD25, and/or CD30**

Did You Know?

The majority of cases are non-advanced (indolent or smoldering SM) occurring in ~90% of patients; advanced cases (aggressive, SM with an associated hematologic neoplasm, or mast cell leukemia) are associated with decreased overall survival[9]
Patients experience significant symptom burden with poor quality of life that can result in a reduced ability to work, higher rates of health care visits, polypharmacy, and severe pain[3]

Identification of SM Subtype

If SM is confirmed, proceed to identification of SM subtype[11,12]:

Indolent SM (non-advanced):
Meets the general criteria for systemic mastocytosis; <2 B-findings*; No C-findings¥; Low mast cell burden; No evidence of an associated hematologic neoplasm; Skin lesions are frequently present

Smoldering SM (non-advanced):
Meets the general criteria for systemic mastocytosis; ≥2 B-findings; No C-findings; No evidence of an associated hematologic neoplasm; Does not meet the criteria for mast cell leukemia

Aggressive SM (advanced):
Meets the general criteria for systemic mastocytosis; ≥1 C-finding; Does not meet the criteria for mast cell leukemia; Skin lesions are usually absent

SM with an associated hematologic neoplasm (advanced):
Meets the general criteria for systemic mastocytosis; Meets the criteria for an associated neoplasm

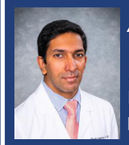
Mast Cell Leukemia (advanced):
Bone marrow aspirate smears show ≥20% mast cells; In classic cases, mast cells account for ≥10% of the peripheral blood white blood cells, but the aleukemic variant (in which mast cells account for <10%) is more common; Skin lesions are usually absent; Mast cell variants include:

- Acute MCL [≥1 C-finding(s)] vs. chronic MCL (no C-findings)
- MCL with an AHN vs. MCL without an AHN
- Primary (de novo) vs. secondary MCL (arising from another SM variant)

*B-Findings: Indicate a high burden of MCs and expansion of the neoplastic process into multiple hematopoietic lineages, without evidence of organ damage
¥C-Findings: Are indicative of organ damage produced by MC infiltration (should be confirmed by biopsy if possible)

NCCN Guidelines[13]: Systemic Mastocytosis Treatment Recommendations

Indolent & smoldering SM	Agressive SM	SM with an associated hematologic neoplasm	Mast Cell Leukeima
• Referral to specialized centers • Patient education • Avoiding triggers • Use of epinephrine to manage anaphylaxis • Anti-mediator drug therapy • Clinical trial • Avapritinib for ISM	• ISM and SSM treatment options • Clinical trial • Avapritinib (if platelets ≥50 x 10^9/L) or midostaurin • Cladribine or peginterferon alfa-2a ± prednisone	• ISM and SSM treatment options • Avapritinib (if platelets ≥50 x 10^9/L) or midostaurin • Other recommended regimens: cladribine or peginterferon alfa-2a ± prednisone • Immedate treatment requirement or on progression: AHN-directed therapy including consideration of allogenic HCT with concurrent management of SM	• ISM and SSM treatment options • Avapritinib or midostaurin • Other recommended regimens: cladribine • AHN-directed therapy (including multiagent chemotherapy) • Consider evaluation for allogeneic HCT



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ABOUT CORNERSTONE
Founded in 2016, Cornerstone Specialty Network's mission is to provide value to Community Oncology practices in order to help maximize the quality of patient care. **To learn more or to register for one of its programs, visit cornerstoneoncology.com**

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