# Diagnostic Criteria and Classification of Mastocytosis in 2014

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**KEYWORDS**

• Mastocytosis • Diagnosis • Classification • World Health Organization • c-kit • Tryptase

**KEY POINTS**

- The diagnosis of mastocytosis in skin is established by presence of characteristic maculopapular skin lesions and confirmed by skin biopsy.
- Systemic mastocytosis should be diagnosed based on World Health Organization (WHO) criteria. Presence of unexplained symptoms of mast cell activation should prompt the pathologic investigation; however, the diagnosis cannot be based on symptoms alone.
- According to WHO, mastocytosis is classified into 7 categories, with distinct clinicopathologic and prognostic features that guide the therapy.
- Tryptase level greater than 20 ng/mL is associated with systemic mastocytosis. However, lower tryptase levels can be seen in patients with cutaneous mastocytosis, monoclonal mast cell activation syndrome, and systemic mastocytosis with limited bone marrow involvement.
- More than 90% of adults and 80% of children with mastocytosis are detected to have somatic gain of function mutations in c-kit. In most patients with systemic mastocytosis, the c-kit mutation D816V is detectable.

## DEFINITION AND OVERVIEW OF CATEGORIES

Mastocytosis is a disorder characterized by accumulation of pathologic mast cells in tissues, which is accompanied by symptoms of mast cell activation in most patients.[1–4] Most commonly affected tissues are skin, bone marrow, and gastrointestinal tract, followed by liver, spleen, and lymph nodes. Mastocytosis can affect both children and adults. In children, it commonly presents with skin lesions of urticaria

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pigmentosa (UP) or mastocytomas within the first year of life.[5–7] Mastocytosis diagnosed in infancy has a good prognosis; there is no evidence of pathologic mast cell accumulation in tissues other than skin (cutaneous mastocytosis), and most patients experience resolution or fading of skin lesions by adolescence. In contrast, adult-onset mastocytosis is almost always associated with bone marrow involvement and has a persistent course. When mastocytosis is present in any extracutaneous tissue (proved by biopsy) and shows multifocal or diffuse organ infiltration, it is termed systemic mastocytosis (SM). SM is a heterogeneous group of disorders with variable prognosis.[8] Most patients have indolent SM (ISM), meaning that bone marrow examination shows abnormal mast cell collections but no other hematologic disease, and there is no evidence of end-organ damage attributable to mast cell infiltration. Patients with ISM have a comparable life expectancy with the general age-matched population.[9–11] Up to 20% of patients with SM may have a second bone marrow disease, usually with myeloproliferative or myelodysplastic features. These patients have SM associated with a hematologic non–mast cell clonal disease (SM-AHNMD). The prognosis in these patients depends on the course of the AHNMD.[10] A few patients (approximately 5%) have evidence of end-organ damage caused by mast cell infiltration (aggressive SM [ASM]), in whom the disease follows an accelerated course resembling a malignancy.[12,13] Mast cell leukemia (MCL) is a rare subset of SM, which is diagnosed when mast cells in bone marrow aspirate smears are greater than 20%.[14,15] In several of these cases, circulating mast cells are found. Mast cell sarcoma (MCS) and extracutaneous mastocytosis are extremely rare variants with solid mast cell tumors, bearing malignant and benign pathologic features, respectively.[16]

## DIAGNOSIS

Mastocytosis commonly comes to clinical attention in one of the following clinical scenarios:

1. The patient (or parents if the patient is a child) notices the hyperpigmented skin lesions of UP (or mastocytoma in a child). Sometimes, these lesions may be noticed in dermatology evaluations for other purposes rather than by patients themselves, because they may resemble freckles earlier in the course.
2. The patient presents with symptoms of mast cell activation such as recurrent flushing, hypotension, near syncope or syncope, abdominal cramps, and diarrhea. Anaphylaxis is suspected, but an allergy evaluation often does not identify a culprit. A variation of this presentation involves patients who experience severe systemic reactions to Hymenoptera stings. Curiously, urticaria and angioedema are not commonly seen in mast cell activation episodes in mastocytosis.
3. The patient is detected to have hematologic abnormalities such as cytopenias or increased white blood or platelet counts, liver or spleen enlargement, fatigue, and weight loss, prompting a hematologic workup.
4. The patient may be detected to have sclerotic or lytic bone lesions in imaging studies, raising concern for metastatic disease.
5. A rare first presentation is osteoporosis and pathologic bone fractures (commonly vertebral compression fractures). This finding should raise suspicion in younger patients (especially males) who do not otherwise have any risk factors for osteoporosis.
6. The patient is referred because of nonspecific gastrointestinal symptoms suggestive of colitis and unexplained splenomegaly, and the hematologic evaluation shows mastocytosis.