Mast Cell Disease

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Mast cell disease, or mastocytosis, includes a variety of disorders that are characterized by the presence of mast cell aggregates in tissue sections and range from isolated, indolent proliferations to systemic, aggressive disorders. The WHO classification of mastocytosis (Table 1) separates cutaneous and systemic forms and provides criteria for the subclassification of the various systemic forms of the disease. While the morphologic detection and immunophenotypic confirmation of mast cell aggregates in tissue sections is essential for diagnosis, subclassification of cases into systemic mastocytosis subtypes requires correlation with a variety of clinical and other laboratory features (Table 2). Morphologically, mast cells can range from aggregates of round cells with finely granular pink cytoplasm to more spindled cells with associated fibrosis (often paratrabecular in the bone marrow). Mast cells are often accompanied by eosinophils and small lymphocytes and may be overlooked due to these other cellular components. On aspirate smears, mast cells are most easily identified in the central portion of marrow particles as round or spindled cells with fine basophilic granules that obscure the nucleus. Spindled and more atypical mast cell features tend to correlate with the more aggressive clinical syndromes, but morphologic features alone are not adequate for subclassifying the mast cell disorders.

Cutaneous Mastocytosis

While various types of mast cell disease may involve the skin, the diagnosis of cutaneous mastocytosis is reserved for cases with no systemic involvement, including no elevation of total serum tryptase or organomegaly. Urticaria pigmentosa, or maculopapular cutaneous mastocytosis, is the most common form of cutaneous mastocytosis. It may occur in children or adults. The mast cell infiltrate is often more subtle in adults and may require examination of multiple sections for diagnosis. The lesions have elongated or spindled mast cells, often associated with small vessels, in the papillary and reticular dermis. Diffuse cutaneous mastocytosis occurs almost exclusively in children without the characteristic maculopapular rash of urticaria pigmentosa. The skin may be more smooth or thickened and red. The mast cell infiltrate generally forms a band in the papillary and upper reticular dermis. Mastocytoma of the skin is a single lesion, most often on the trunk or wrist of infants. Mast cells without atypia fill the papillary and reticular dermis and may extend into the deep dermis and subcutaneous adipose tissue. In children, cutaneous mastocytosis is an indolent disorder that usually regresses spontaneously around puberty. In adults, regression is less common and careful staging is warranted since most adults presenting with skin lesions will actually have systemic disease. However, the presence of skin lesions, even with systemic disease, usually portends an indolent clinical course.

Systemic Mastocytosis

A diagnosis of systemic mastocytosis requires detection of multifocal mast cell aggregates in tissue sections (major criterion) as well as one minor criterion or, in the absence of tissue section aggregates, identification of three minor criteria (Table 2). Subclassification of systemic mastocytosis requires further correlation with clinical, morphologic and laboratory findings and these are designated as “B” or “C” findings (Table 3).

Indolent systemic mastocytosis meets criteria for systemic mast cell disease, but has no B or C findings and no evidence of another hematologic malignancy. Skin lesions are usually present.
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As the name implies, these cases are clinically indolent, and this is the most common form of systemic mast cell disease.

*Systemic mastocytosis with associated clonal, hematological non-mast cell lineage disease* meets criteria for systemic mastocytosis as well as being associated with another hematologic malignancy in the WHO classification. This occurs in almost one third of patients with systemic mast cell disease and the associated tumor is usually a myeloid malignancy, which may include myelodysplasia, chronic myeloproliferative disorders, mixed myeloproliferative and myelodysplastic syndromes, acute myeloid leukemia and chronic eosinophilic leukemia. Associated lymphoid malignancies are most often multiple myeloma, but chronic lymphocytic leukemia, acute lymphoblastic leukemia and hairy cell leukemia may also occur. The prognosis of these patients is usually based on the non-mast cell disorder. Rare cases will not have identifiable mast cell disease at diagnosis, but mastocytosis may become apparent in the post-therapy bone marrow.

*Aggressive systemic mastocytosis* meets criteria for systemic mastocytosis as well as having one or more of the C findings (Table 3) indicating organ dysfunction due to mast cell infiltration. These patients do not have an associated hematologic malignancy or evidence of mast cell leukemia. A provisional subvariant termed *lymphadenopathic mastocytosis with eosinophilia* presents with lymphadenopathy and eosinophilia and should be differentiated from chronic eosinophilic leukemia. Patients with aggressive systemic mastocytosis have a short survival, usually of only weeks to months.

*Mast cell leukemia* is a form of systemic mastocytosis with a diffuse marrow infiltration (>20%) of atypical, immature mast cells in the bone marrow with 10% or more mast cells in the peripheral blood. An aleukemic variant is also proposed. Both have the similarly dismal prognosis of aggressive systemic mastocytosis.

**Other Presentations of Mastocytosis**

*Mast cell sarcoma* is an extremely rare localized disorder that occurs in the absence of skin lesions or other systemic disease. The mast cells are highly atypical with a destructive growth pattern. A leukemic phase may develop in these patients and they have a generally poor prognosis.

*Extracutaneous mastocytoma* is most commonly reported in the lung without skin lesions or other systemic disease. In contrast to mast cell sarcoma, the lesional cells are not atypical and do not show a destructive growth pattern.

**Special Stains and Immunophenotyping in Mastocytosis**

Normal mast cells mark with chloracetate esterase and toluidine blue, but the later stain is pH dependent in mastocytosis and these stains are less helpful than more specific immunophenotypic studies. Mast cells express CD33, CD43, CD68, CD117 and tryptase. Tryptase is the most lineage specific of these markers, but may show high background staining in some cases. Neoplastic mast cells also express CD2 and/or CD25, with the later more easy to detect in most cases. A panel of CD117, tryptase and CD25 is recommended for most cases to aid in confirming the mast cell lineage of the proliferation and to potentially identify an aberrant immunophenotype (CD25-positive).
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Genetics of Mastocytosis
Point mutations of the tyrosine kinase receptor gene KIT are the most common genetic abnormality in mastocytosis and the most common mutation results in a substitution of valine for aspartate at codon 816 of exon 17, termed Asp816Val or D816V. This mutation is found in over 90% of patients with systemic mastocytosis. Other mutations described include tyrosine or phenylalanine for aspartate at codon 816, and lysine for glutamic acid at codon 839. KIT mutations, however, are not specific for mastocytosis and are reported in other disease. Even the D816V mutation of this gene is not disease specific and may occur in some seminomas and some core binding factor acute myeloid leukemias. For this reason, detection of the mutation represents only a minor diagnostic criterion.

Therapy for Mastocytosis
Patients with mastocytosis are treated symptomatically and no curative therapies for the aggressive disease types are currently available. Some success in reducing the mast cell burden has been reported with alpha interferon and with cladribine (2-CdA). Tyrosine kinase inhibitors directed at the KIT mutation may be useful in some patients. However, the D816V mutation of KIT results in resistance to imatinib mesylate. Ongoing trials with other tyrosine kinase inhibitors, such as PKC 412, are underway in the hope of directly impacting the molecular defect of this disease.

Table 1. WHO Classification of Mastocytosis
Cutaneous Mastocytosis
   Urticaria pigmentosa/ maculopapular cutaneous mastocytosis
   Diffuse cutaneous mastocytosis
   Solitary mastocytoma of skin
Indolent Systemic Mastocytosis
Systemic Mastocytosis with Associated Clonal, Hematological Non-mast-cell Lineage Disease
Aggressive Systemic Mastocytosis
Mast Cell Leukemia
Mast Cell Sarcoma
Extracutaneous Mastocytoma

Table 2. Criteria for Systemic Mastocytosis
Major
Multifocal, dense mast cell infiltrates (≥15 cells) in tissue sections confirmed by tryptase or other special stains

Minor
   a. >25% spindled, immature or atypical mast cells in tissue sections or bone marrow aspirate smears
   b. Detection of KIT D816V mutation
   c. Expression of CD117 with CD2 and/or CD25
   d. Serum total tryptase persistently >20 ng/ml (unless there is an associated clonal myeloid disorder in which case this parameter is not valid)

Diagnosis requires major and one minor or three minor criteria
Table 3. B and C Findings in Mastocytosis

B Findings
1. >30% bone marrow mast cells in focal, dense aggregates and/or serum total tryptase level >200 ng/ml
2. Signs of dysplasia or myeloproliferation in non-mast cell lineage, but insufficient criteria for a definitive diagnosis of a hematopoietic neoplasm by WHO, with normal or only slightly abnormal blood counts
3. Hepatomegaly without liver function impairment, and/or palpable splenomegaly without hypersplenism, and/or palpable or visceral lymphadenopathy

C Findings
1. Bone marrow dysfunction manifested by one or more cytopenia (ANC <1.0x10^9/L, HBG <10g/dl, or PLTs <100x10^9/L) but no frank non-mast cell hematopoietic malignancy
2. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension
3. Skeletal involvement with large-sized osteolysis and/or pathological fractures
4. Palpable splenomegaly with hypersplenism
5. Malabsorption with weight loss due to GI mast cell infiltrates

Selected References

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