Mast Cell Disease Assessment by Flow Cytometric Analysis

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KEYWORDS

• Flow cytometry • Mast cell disease • Mastocytosis
• Immunophenotype of mast cells

KEY POINTS

- Mast cells are present at low frequency in the bone marrow and require highly sensitive and standardized techniques for adequate acquisition of cells by flow cytometry.
- Mast cells can be identified by flow cytometric immunophenotypic analysis based on bright CD117 expression and variable side scatter, and neoplastic mast cells can be identified based on aberrant expression of CD25 and/or CD2, but not in all cases.
- Mast cells in systemic mastocytosis typically demonstrate event clustering within the flow cytometric CD117 x SSC gate, which can be assessed using statistical and/or clustering algorithms.
- CD30 may be helpful as an additional marker to identify neoplastic mast cells in systemic mastocytosis, including cases of well-differentiated systemic mastocytosis.

INTRODUCTION: MAST CELLS AND MAST CELL DISORDERS

Mast cells play an essential role in the innate immune system and allergic reactions.[1,2] Upon cross-linking of the surface high-affinity immunoglobulin E (IgE) receptor (FcεRI), multiple signaling pathways are initiated that lead to degranulation of cytoplasmic contents including histamine, heparin, and proteases, de novo synthesis of arachidonic acid metabolites, and production of various cytokines and chemokines.[1,3] Release of these mediators leads to clinical symptoms such as flushing, pruritus, urticaria, angioedema, bronchoconstriction, increased vascular permeability, and anaphylaxis.[1] Patients who present with this constellation of symptoms may be evaluated for an underlying mast cell disorder.

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Mast cell disorders include both primary and secondary disorders. Primary mast cell disorders, which fall under the category of mastocytosis, are a heterogenous group, all characterized by an accumulation of abnormal populations of mast cells that express aberrant cell markers and genetic mutations, in at least 1 organ. These disorders range in severity from benign entities involving skin to malignant rapidly progressive malignant neoplasms, such as mast cell sarcoma (**Box 1**).

Mastocytosis is defined in the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia[4] as 3 distinct entities: cutaneous mastocytosis, systemic mastocytosis (SM), and mast cell sarcoma (MCS). SM is subcategorized into 5 separate entities: indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL, **Box 1**). The 2008 World Health Organization (WHO) classification of tumors of haematopoietic and lymphoid tissues established well-defined criteria for the diagnosis of SM that include 1 major criterion (multifocal clusters of >15 mast cells in extracutaneous organs) and 4 minor criteria (atypical mast cell morphology, aberrant CD2 and/or CD25 expression on mast cells, presence of D816V KIT mutation, or persistently elevated serum tryptase levels of >20 ng/mL, **Box 2**).[5] The diagnosis of SM can be made when the major criterion and 1 minor criterion or at least 3 minor criteria are present. In addition to the established variants of SM, a potential new variant of SM has recently been described, termed well-differentiated systemic mastocytosis (WDSM), in which the mast cells harbor the D816V KIT mutation but are of normal morphology and do not express aberrant CD2 or CD25.[6–9]

Secondary mast cell disorders include several entities under the broad category of mast cell activation syndromes. In these disorders, mast cells are present in normal numbers but are hyper-responsive and fulfill 1 or more of the minor diagnostic criteria for systemic mastocytosis.[1,10,11] Monoclonal mast cell activation syndrome requires the presence of 1 or 2 minor criteria for mastocytosis.[1] Additionally, patients with idiopathic anaphylaxis have been demonstrated to harbor the D816V KIT mutation and aberrantly express CD25 on their mast cells.[10] Other mast cell-driven processes such as allergic disorders, physical urticarias, chronic autoimmune urticaria, and

Box 1
Word Health Organization (WHO) classification of mastocytosis (2016 revision to the 2008 WHO classification)

1. Cutaneous mastocytosis (CM)
2. Systemic mastocytosis
   a. Indolent systemic mastocytosis (ISM)
   b. Smoldering systemic mastocytosis (SSM)
   c. Systemic mastocytosis with an associated hematological neoplasm (SM-AHN)[a]
   d. Aggressive systemic mastocytosis (ASM)
   e. Mast cell leukemia (MCL)
3. Mast cell sarcoma

[a] Equivalent to the previously described category "systemic mastocytosis with an associated clonal hematological non-mast cell lineage disease (SMAHNMD)"

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