Bone Marrow Expression of Mast Cell Disorders

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KEYWORDS

• Mast cells • Mastocytosis • Flow cytometry • Bone marrow • Cell purification • Diagnosis • KIT mutation • Prognosis

KEY POINTS

- Mast cell disorders constitute a group of heterogeneous diseases that should be managed in specialized reference centers, in order to increase patient access to high-quality diagnostic tests and treatment.
- To establish the correct diagnosis and prognosis of the disease, highly specialized laboratory diagnostic tests should be applied in the diagnostic workup in suspected systemic mastocytosis.
- Multiparameter flow cytometry stands as the most sensitive technique to determine the grade of involvement of the bone marrow, together with the exact diagnosis, subtype, and prognosis of mastocytosis.
- Sensitive approaches for detecting KIT mutation in highly purified bone marrow mast cells are mandatory to avoid false negative results, moreover when a pathologic low bone marrow mast cell burden is suspected.

INTRODUCTION

The World Health Organization (WHO) recently updated the classification of mastocytosis[1–3] in the following categories:

I. Cutaneous mastocytosis (CM) when it is limited to the skin;
II. Systemic mastocytosis (SM) when abnormal mast cells (MCs) are located in extracutaneous organs, including the bone marrow (BM); it is divided into indolent

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SM (ISM), smoldering SM, SM with an associated hematologic (non-MC lineage) neoplasm (SM-AHN), aggressive SM (ASM), and mast cell leukemia (MCL);

III. MC sarcoma. Furthermore, 2 other subvariants of mastocytosis have been recognized:

1. Well-differentiated forms with cutaneous and systemic (WDSM) involvement[4]; these forms show unique features that require specific diagnostic criteria;
2. ISM in the absence of skin lesions (ISMs−).[5–7]

According to the WHO criteria,[2,3] the diagnosis of SM is based on the coexistence of one major criterion (presence of multifocal dense aggregates of $\geq$15 MCs in BM biopsies and/or in sections of other extracutaneous organs) plus one minor criterion or simultaneous detection of 4 minor criteria:

A. Identification of greater than 25% of atypical MCs on BM smears or infiltrates of spindle-shaped MCs on sections of visceral organs,
B. KIT point mutation at codon 816 in the BM or another extracutaneous organ,
C. MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25,
D. Baseline serum tryptase levels greater than 20 ng/mL.

In clinical practice, the suspicion of an underlying MC disorder is based on the presence of the typical skin lesions of mastocytosis or in patients without skin lesions presenting with systemic symptoms of MC activation (MCA) (eg, anaphylaxis).[8]

Despite the great relevance and efficiency of the WHO criteria in the diagnosis of SM, frequently in nonaggressive categories of SM, MCs represent a very small proportion of all nucleated BM cells (<10^{-3} BM MCs, as assessed by flow cytometry).[9,10] Along this line, BM MC aggregates are not found in 30% to 54% of the ISMs− patients and serum tryptase levels are frequently less than 20 ng/mL in 31% to 38% of the ISMs− cases (anaphylaxis elicited by other triggers vs insects, respectively).[11] Therefore, it is mandatory to apply highly sensitive and specific methodological approaches to the study of BM MCs, including detailed cytologic analysis of BM smears, flow cytometry immunophenotyping using specific strategies for detecting MCs present at low frequencies,[12,13] detection of KIT mutations in highly purified BM MCs,[14] as well as the rational combination of the SM criteria in the routine diagnosis of SM,[10,15] in order to improve the diagnostic efficiency and quality as previously reported.[16]

Of note, the sensitivity and specificity of the methodological approaches used in the diagnosis of ISMs− contribute to explain the differences in the percentage of SM among adults presenting with systemic symptoms of MCA in the absence of skin lesions described in different reports.[7,17–19] In addition, different terms such as (mono) clonal MC activation syndrome (MMAS)[8,18,19] or primary MC activation syndrome[20] or clonal MC activation disorder (c-MCAD)[7] emerged to name those cases who do not meet the WHO criteria for SM, despite KIT mutated clonal MCs that usually express CD25 are found (**Fig. 1**).

The mast cell activation syndrome (MCAS) includes a heterogeneous group of diseases that are characterized by systemic symptoms secondary to the release of MC mediators that may or may not have a known trigger, may or may not present specific immunoglobulin E (IgE) antibodies in response to that trigger, and are associated with normal or elevated baseline tryptase levels in the absence of skin lesions of mastocytosis.[8,21] The diagnosis and classification of MCAS are based on previous described clinical and laboratory criteria.[8] The Spanish Network of Mastocytosis (REMA) supports that the most relevant fact to classify the MCAS is the presence versus absence of clonal MCs (based on the expression of $CD25^+$ and/or KIT mutation).[21] When