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The 2023 Updated Classification and Diagnostic Criteria of Mastocytosis

Nahla AM Hamed*

Professor of Hematology, Faculty of Medicine, Alexandria University, Egypt

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***Corresponding author:** Nahla AM Hamed, Professor of Hematology, Faculty of Medicine, Alexandria University, Egypt

Abstract

Mastocytosis is an uncommon hematologic malignancy characterized by accumulation of abnormal mast cells in various organs or tissues. A somatic point mutation in the KIT gene at codon 816 is detected in more than 90% of patients with systemic Masto cytosis (SM). The 2022 WHO classification continues to recognize three disease types: systemic mastocytosis, cutaneous mastocytosis and mast cell sarcoma. Bone marrow mastocytosis is a new separate subtype of SM. The classification also recognizes well-differentiated systemic mastocytosis, a morphologic pattern that can occur in any SM subtype. Diagnostic criteria for SM have been modified. The expression of CD30 and the presence of any KIT mutation causing ligand-independent activation have been accepted as minor diagnostic criteria. Classical B-findings and C-findings have undergone minor refinements. Most notably, variant allele frequency of D816V mutation ≥ 10% in bone marrow cells or peripheral blood leukocytes is qualified as a B-finding.

Keywords: Mastocytosis; Mast cell sarcoma; Smoldering; Myeloproliferative; Ameliorate; Anaphylaxis; Avapritinib

Abbreviations: SM: Systemic Mastocytosis; AHN: Associated Hematologic Neoplasm; Hαt: Hereditary Alpha-Tryptasemia; BMM: Bone Marrow Mastocytosis; ISM: Indolent SM; MC: Mast Cell; MCL: Mast Cell Leukemia; SSM: Smoldering SM; ASM: Aggressive SM

Introduction

Mastocytosis is a rare hematologic neoplasm characterized by accumulation of abnormal mast cells in various organs or tissues including the skin, bone marrow, liver, spleen, and gastrointestinal tract. It is typically driven by constitutive activation of the KIT receptor. A somatic point mutation in the KIT gene at codon 816 is detected in more than 90% of systemic mastocytosis (SM) patients irrespective of WHO SM subtype. Most patients with advanced SM and D816V have additional somatic mutations involving most frequently TET2, SRSF2, RUNX1, ASXL1, and JAK2. An associated hematologic (usually myeloid) neoplasm may be detected in these patients. Mutations in the juxtamembrane (e.g., V560G), transmembrane (e.g., F522C), or extracellular (e.g., deletion of codon 419 on exon 8 or A502_Y503dup in exon 9) domains, are rare activating KIT alterations which are detected in less than 1% of advanced SM cases and are enriched in indolent SM cases [1]. The pathology of mastocytosis is complex [1]. The clinical presentation of mastocytosis is heterogeneous, ranging from skin-limited disease (cutaneous mastocytosis), particularly in pediatric cases and commonly regress spontaneously at puberty, to a more aggressive variant that is generally seen in adult patients and may be associated with multiorgan dysfunction/failure (SM) and has shortened survival [2]. The clinical features of mastocytosis may be modulated by the presence of comorbidities. Significant comorbidities include IgE dependent allergies, vitamin D deficiency, and psychiatric or mental problems [1].

Classification

The 2022 WHO classification continues to include three types: cutaneous mastocytosis (CM), systemic mastocytosis (SM) and mast cell sarcoma (MCS) [1].

Systemic Mastocytosis (SM)

Systemic mastocytosis (SM) is subdivided into six subtypes. The diagnosis of these variants of SM requires correlation with B ('burden of disease') and C ('cytoreduction-requiring') findings [2]. Organ damage caused by an AHN or by other etiologies (such as infection or therapy-induced) does not count as a C-finding [3]. These subtypes are [3]

i. **Bone marrow mastocytosis (BMM):** a new separate subtype of SM characterized by absence of skin lesions, no B-findings or C-findings and a basal serum tryptase below 125 ng/ mL [1],

ii. **Indolent SM (ISM):** no or one B-finding and no C-finding,

iii. **Smoldering SM (SSM):** presence of ≥2 "B-findings,

iv. **Aggressive SM (ASM):** at least 1 C-finding must be documented,

v. **SM-associated hematologic neoplasm (SM-AHN):** myeloid neoplasms such as myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), MDS/ MPN overlap-neoplasms, chronic myelomonocytic leukemia, chronic eosinophilic leukemia, and acute myeloid leukemia should be qualified as AHN [3]. Lymphoid neoplasms are a rare association. Pre/sub diagnostic clonal conditions, such as monoclonal gammopathy of undetermined significance or monoclonal B lymphocytosis, are not considered AHN [3]. The diagnosis of SM-AHN can sometimes only be established after successful cytoreductive therapy. Therefore, it is recommended to apply all SM criteria again in all patients with a KIT D816V-mutated myeloid neoplasm after (successful) cytoreduction [3].

vi. **Mast cell leukemia (MCL) (2):** WHO classification remains unchanged and divides MCL into primary MCL (no previous SM known) and secondary MCL following a previous (lower grade) SM. MCL can be further classified into a classical (leukemic) form (MC ≥10% of all leukocytes in PB smears) and a more frequent, aleukemic MCL variant (MC <10% of all leukocytes in PB smears). MCL can be split into acute MCL (C-findings detectable) and chronic MCL (C-findings are undetectable). Patients with chronic MCL have a better prognosis and may respond to treatment with KIT-targeting drugs. However, many of these patients progress over time to acute MCL. MCL can be classified into pure MCL and MCL-AHN where the prognosis is particularly poor [3].

Well-Differentiated Systemic Mastocytosis (WDSM)

A distinct morphologic pattern that occurs rarely in SM. It can occur in any SM type/subtype, including MCL. The bone marrow is usually heavily infiltrated with well-differentiated round and well-granulated mast cells. In most patients, neoplastic mast cells are usually negative for aberrant CD2 and CD25 expression but positive for CD30, and KIT codon 816 mutation is not detected [1].

Diagnostic Criteria

According to 2016 WHO classification, the diagnosis of SM can be established when at least 1 major and 1 minor or 3 minor SM criteria are fulfilled [3]. The major criterion is the presence of multifocal MC clusters (≥15 mast cells in aggregates) in the bone marrow and/or extracutaneous organs. Minor diagnostic criteria include elevated serum tryptase level >20 ng/mL, ≥25% of all mast cells are atypical, MC expression of CD25/CD2/CD30, and presence of activating KIT mutations [2].

Fallacies in Diagnosis

Serum tryptase level

SM as well as several other conditions are associated with an elevated serum tryptase level. The following restrictions are proposed:

(1) Measurement of basal serum tryptase level (in a symptom-free interval) only can be qualified as a minor SM criterion (2) the basal serum tryptase level does not qualify as a SM criterion when an AHN is present. AHN cells may produce tryptase (3) the basal tryptase level should be corrected for the presence of hereditary alpha-tryptasemia (HαT) in patients with known HαT. One suggested approach to correct for HαT is to divide the basal tryptase level by one plus the number of extra alpha tryptase gene-copies [3].

Mast cell morphology

The spindle-shaped morphology of mast cells does not count as an SM criterion when mast cells are adjacent to (lining) blood vessels, endosteal surfaces, nerve cells, or fat cells [3]. In the bone marrow smear, an atypical morphology of mast cells does not count as SM criterion when mast cells are located in or adjacent to bone marrow particles [2].

Modification Of Minor Diagnostic Criteria In 2022 WHO Classification

Minor diagnostic criteria of SM have been modified in 2022 WHO classification. The presence of any KIT mutation causing ligand-independent activation and CD30 expression have been introduced as minor diagnostic criteria [1]. CD30 is a transmembrane receptor, normally not expressed by mast cells. CD30 has higher diagnostic value in SM than other immunohistochemically detectable molecules since CD30 expression in MC is strongly associated with SM and is absent in other myeloid neoplasms [4].

Proposed modifications in B-findings and C-findings

Classical B-findings and C-findings have undergone minor refinements in 2022 WHO classification. Most notably, D816V mutation with a high variant allele frequency (VAF) ≥ 10% in bone marrow cells or peripheral blood leukocytes should be qualified as B-finding as it indicates a high MC burden or a surrogate of multilineage involvement in SM [1].

Differential Diagnosis

Myelomastocytic leukemia (MML)

It is an important differential diagnosis of MCL. In these patients, neoplastic MC (≥10% in BM or blood smears) are derived from neoplastic stem cells of an underlying myeloid neoplasm. KIT mutations outside of codon 816 may be found in a subset of these patients. SM criteria are not fulfilled in these patients. Based

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on updated SM criteria, some of these cases may be reclassified as true MCL over time [3].

"Prediagnostic ISM" or "monoclonal mast cell activation syndrome" (MCAS)

These patients display recurrent symptoms of systemic mast cell activation of varying severity with concurrent increase in MC mediator release. Patients have clonal/neoplastic mast cells (i.e., mutated KIT gene and/or CD25 expression), but they do not meet criteria for SM (only 1 or 2 minor criteria satisfied, and no skin involvement). These patients generally have normal or slightly elevated baseline serum tryptase level. While the clinical characteristics of this entity may be indistinguishable from ISM, its true natural history remains to be defined [2].

Prognosis of SM

Several risk models are available to help to assign prognosis in SM patients. The recently established prognostic scoring systems, include the international prognostic scoring system for Mastocytosis (IPSM), the molecular-adjusted revised prognostic score, the Red Española de Mastocytosis score, and the global prognostic score [3]. In the IPSM model, the nonadvanced group was classified according to age (>60) and serum alkaline phosphatase (>100 u/L) value as intermediate risk group 1 and 2. Patients without these risk factors were defined as the low-risk group. In advanced systemic mastocytosis group, age ≥60 years, tryptase ≥125 ng/mL, leukocytes ≥16× 10^3 /μL, hemoglobin ≤11g/dL, platelets ≤100× 10^3 /μL and skin involvement are independent prognostic factors for overall survival. Patients are grouped into the following subgroups: advanced systemic mastocytosis 1 (AdvSM-1) if they have no risk factors, AdvSM-2 for those with one risk factor, AdvSM-3 for individuals with two or three risk factors, and AdvSM-4 in patients with four or five risk factors [4].

Management

i. **ISM and SSM:** treatment goals for these patients are primarily directed towards anaphylaxis prevention, symptom control and osteoporosis treatment.

ii. **Advanced SM:** these patients frequently need MC cytoreductive therapy to ameliorate disease related organ dysfunction. High response rates have been seen with small-molecule inhibitors including midostaurin or avapritinib that target mutant-KIT. Other options for MC cytoreduction include cladribine or interferon-α.

iii. **SM-AHN:** treatment of these patients primarily targets the AHN component, particularly if an aggressive disease such as acute myeloid leukemia is present. Allogeneic stem cell transplant can be considered in such patients, or in those with relapsed/refractory advanced SM [5].

iv. **KIT inhibition**

Imatinib has a limited therapeutic role in SM [5]. Initial reports showed that the rare KITD816V negative cases were only responsive to first line TKI imatinib. New TKIs with activity against the KITD816V mutation, such as midostaurin or avapritinib have changed the management of this disease [6].

v. **Avapritinib (BLU-285):** an oral small molecule kinase inhibitor that was approved by FDA as first-line treatment of adult patients with advanced SM, including those with ASM, SM-AHN and MCL in June 2021. Avapritinib selectively inhibits activation-loop mutants of KIT, including KITD816V. Avapritinib also inhibits the analogous mutation in PDGFRA, namely D842V. The drug appears highly selective with limited inhibitory activity outside of KIT and PDGFRA kinases [2]. Other potential targets for avapritinib include wild-type KIT, PDGFRβ, and CSFR1. Avapritinib is roughly tenfold more potent than midostaurin because of higher potency against the D816V mutant form of KIT [7].

Treatment responses in ASM

Treatment responses in ASM were evaluated based on the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response [8].

Complete response (CR): disappearance of mast cell infiltration in the affected organs, decrease in serum tryptase level below 20 ng/mL, disappearance of C findings and peripheral blood count remission.

Partial response (PR): reduction by ≥50% in neoplastic MCs in the affected tissue, reduction of serum tryptase level by ≥50% and resolution of one or more biopsy proven or suspected SM-related organ damage.

Progressive disease (PD): deterioration of the prior laboratory abnormality, decrease in albumin (increase in severity or decrease more than 0.5 g/dL), new transfusion dependence or increase in the average transfusion frequency, increase in spleen and liver size.

Clinical improvement (CI): presence of at least one of the hematological or non-hematological response criteria that did not meet CR, PR or progressive disease (PD).

Stable disease (SD): patients who did not meet previous response criteria [9].

Conclusion

The fundamental WHO classification of mastocytosis remains unchanged. Diagnostic criteria for mastocytosis and its variants were refined based on recent developments in new genetic and immunological markers. An updated global classification of MC disorders, including MCAS is also proposed.

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