Review

Systemic Mastocytosis: Clinical Update and Future Directions

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Abstract

Systemic mastocytosis (SM) is defined as the accumulation of abnormal mast cells (MC) in 1 or more extracutaneous tissues. Symptoms are due to either MC activation or organ infiltration and vary depending on disease subtype. More benign forms of SM, such as indolent SM, result in a life expectancy similar to the general population, while more aggressive subtypes, such as MC leukemia (MCL), have a median survival measured on the order of months. Treatment of indolent SM is directed at controlling the symptoms associated with MC activation. In advanced forms, such as aggressive SM and MCL, agents targeting MC proliferation such as KIT tyrosine kinase inhibitors, cladribine, and thalidomide may be provided. Newer agents based on preclinical rationale are also being actively investigated. However, the only potentially curative therapy for aggressive SM/MCL remains hematopoietic stem cell transplantation. Given that SM is a relatively rare disease, clinicians are often underprepared to evaluate, diagnose, and effectively treat this clinically heterogeneous condition. Here we seek to familiarize clinicians with this orphan disease and review current and future treatment approaches.

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Introduction

Mastocytosis is a disease characterized by the pathologic accumulation of mast cells (MC) in 1 or more tissues. There are 2 major forms: cutaneous mastocytosis (CM) and systemic mastocytosis (SM). CM is usually a disease of childhood and typically resolves by puberty, while SM is found in adults and is often persistent.[1] Although MC were known to invade the skin soon after their discovery in 1879,[2] it was not until 1949 that extracutaneous involvement was first reported.[3] These patients can experience a wide range of symptoms, such as fatigue, weight loss, gastrointestinal upset, cytopenias, and psychiatric symptoms. With aggressive forms of the disease, a second hematologic process, such as a myeloproliferative neoplasm (MPN), myelodysplastic syndrome, or acute leukemia, may coexist.[4] SM remained a somewhat nebulous disease until the release of the current classification system, adopted by the World Health Organization (WHO) in 2001.[5,6] However, the diagnosis remains challenging to establish, as mastocytosis is relatively uncommon and many clinicians are not readily accustomed to diagnosing and treating SM. The clinical course of SM can range from benign to life-threatening depending on subtype, and there are no consensus treatment guidelines. In this review, we discuss the various subtypes of SM and propose an algorithm for assessment and treatment.

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Pathogenesis

MC proliferation is dependent on stem cell factor and *KIT,* a proto-oncogene encoding a transmembrane receptor tyrosine kinase (Kit). Kit (CD117), expressed widely on hematopoietic stem cells and multipotential progenitor cells, is integral to differentiation of both myeloid and lymphoid lineages, but it is down-regulated in all mature lineages except in the case of MC. Therefore, Kit signaling is necessary for growth, differentiation, and function of human MC.[7] Activating mutations of *KIT* have been identified in the majority of patients with SM, most commonly in the form of a valine substitution for aspartate at codon 816 (D816V).[8,9] This point-activating mutation lies within the activation loop domain and causes a conformational change in the juxtamembrane region, allowing departure from the kinase domain. *KIT*D816V results in constitutive receptor dimerization and signaling in the absence of stem cell factor.[10] Overall, uncontrolled activation of the Kit receptor leads to increased production of MC and the accumulation of MC in extracutaneous organs, which can result in organ failure and even early death.

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Neoplastic MC development is essentially governed by the Stat5-PI3K-Akt signaling cascade, downstream of the mutated *KIT*.[11] The acquisition of this somatic mutation appears to occur as a late event in the advanced forms of the disease, specifically in SM with an associated clonal hematologic non-MC lineage disease (SM-AHNMD), where there is a concurrent myeloid neoplasm. In this subtype, the mutation acts as a phenotypic modifier toward SM.[12] Other molecular events likely contribute to the pathogenesis of SM. Mutations in the tumor suppressor gene *TET2* have been shown to be frequently present in SM and may be associated with a more aggressive disease phenotype.[13,14] *ASXL1* mutations have also been shown to negatively affect overall survival in a subset of SM patients.[15] Mutations in components of the splicesome machinery such as *SRSF2* have also been associated with advanced forms of the disease.[16] A recent mutational analysis of 39 patients with *KIT*D816V documented the above-mentioned commonly mutated genes, along with *CBL and RUNX1*. The presence of these additional genetic aberrations were correlated with increased disease severity and reduced overall survival.[17] These and other genetic and epigenetic alterations appear to contribute to the molecular pathogenesis of SM and are of particular interest as potential therapeutic targets.

Diagnosis and Classification

As the understanding of SM has evolved, so too have the classification systems used to describe different subtypes of the disease.[4,18-20] This culminated in 2001 with the release of consensus diagnostic criteria and a classification system that was subsequently adopted by the WHO (Table 1).[5,6] The major criterion is the presence of bone marrow or an extracutaneous organ with multifocal dense infiltrates of > 15 MC. There are 4 minor criteria that are based on cytomorphologic MC findings and biochemical markers: > 25% of MC in infiltrates are spindle shaped or atypical; *KIT*-activating mutation at codon 816 (eg, D816V) in an extracutaneous organ; Kit^+ MC express CD2 and/or CD25; and serum total tryptase concentrations consistently exceed 20 ng/mL. Diagnosis of SM requires either 1 major and 1 minor or at least 3 minor criteria to be fulfilled.[5]

Categorizing SM can assist clinicians in assessing the aggressiveness of the disease in order to determine an appropriate risk adapted treatment strategy (Figure 1). There are 4 major subtypes of SM (Table 2): indolent SM (ISM), SM-AHNMD, aggressive SM (ASM), and MC leukemia (MCL).[5,6] The other forms of WHO-recognized mastocytosis—CM, MC sarcoma, and extracutaneous mastocytoma—will not be discussed in this review.

The specific variant of SM is determined by the presence or absence of B and C findings. B findings indicate MC infiltration or fibrosis of an organ (bone marrow, lymph nodes, liver, spleen) without organ dysfunction. C findings, on the other hand, refer to the MC disease process causing organ dysfunction, such as cytopenias, malabsorption, large osteolyses (with or without pathologic fractures), liver impairment, and resulting ascites (Table 1).[5]

ISM is characterized by the lack of C findings and is the most common subtype of SM.[5,21] Bone marrow examination must exclude MCL and SM-AHNMD and usually shows mature MC with low grade of infiltration (< 30%).[22] ISM has 2 subvariants: isolated bone marrow mastocytosis (BMM) and smoldering SM (SSM). BMM is characterized by the lack of skin lesions and seemingly isolated bone marrow involvement. In SSM, 2 or more B findings are present, representing a higher burden of MC.[5,23] As discussed below, SSM may have an increased risk of disease transformation to a more aggressive form.[24]

AHNMD can develop in a significant portion of patients with SM and represents its own subtype of SM.[5] Essentially, any hematologic malignancy may occur in association with SM, and as noted above, it is often a multigene mutated disease in which *KIT*D816V occurs as a late event and influences the development of SM. However, myeloid neoplasms occur in > 75% of cases,[25] owing to the likely presence of a shared malignant myeloid precursor cell.[26] Lymphoproliferative disorders have also been reported, however, often without a direct causal relationship with the concurrent SM.[27] Diagnosis of

Table 1 Diagnostic Criteria

A.Criteria[a]

1. **Major Criterion**
   Multifocal, dense infiltrates of mast cells (≥15 MCs in aggregates) detected in sections of BM and/or other extracutaneous organs.
2. **Minor Criteria**
   a. In biopsy sections of BM or other extracutaneous organs, > 25% of MCs in infiltrate are spindle shaped or have atypical morphology or, of all MCs in BM aspirate smears, > 25% are immature of atypical.
   b. Detection of activating point mutation at codon 816 of *KIT* in BM, blood or other extracutaneous organ.
   c. MCs in BM, blood or other extracutaneous organs express CD2 and/or CD25 in addition to normal MC markers.
   d. Serum total tryptase persistently exceeds 20 ng/mL (unless there is associated clonal myeloid disorder, in which case this parameter is not valid).

B.Findings

1. BM biopsy shows > 30% infiltration by MCs (focal, dense aggregates) and/or serum total tryptase level > 200 ng/mL.
2. Signs of dysplasia or myeloproliferation in non-MC lineage, but insufficient criteria for definite diagnosis of hematopoietic neoplasm (AHNMD) with normal or slightly abnormal blood counts.
3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpitation or imaging.

C.Findings

1. BM dysfunction manifested by 1 or more cytopenias (ANC < 1.0×10^9/L, hemoglobin < 10 g/dL or platelets < 100×10^9/L) but no obvious non-MC hematopoietic malignancy.
2. Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension.
3. Palpable splenomegaly with hypersplenism.
4. Malabsorption with weight loss due to gastrointestinal MC infiltrates.

Abbreviations: AHNMD = associated hematologic non–mast cell disorder; ANC = absolute neutrophil count; BM = bone marrow; MC = mast cell.
[a]Diagnosis = 1 major + 1 minor OR 3 minor.
Adapted from World Health Organization diagnostic criteria.[6]