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Overview of Diagnostic Procedure of Systemic Mastocytosis

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Abstract: **Systemic mastocytosis (SM) constitutes a stem cell-derived clonal myeloproliferation with obvious mast cell expansion. Medical symptoms include urticaria pigmentosa and mast cell arbitrator release signs (MCMRS) such as anaphylaxis, diarrhea, and presyncope. This review aimed to discuss and evaluate the diagnosis approaches of Systemic mastocytosis also to be able to clear the concepts of diagnosis of this stem cell disorder, we therefore reviewed the clinical manifestations of mastocytosis. PubMed, and Embase databases searches were performed for articles published regarding diagnosis procedures of systemic mastocytosis and the diagnostic criteria and treatment options for this condition using the keywords: systemic mastocytosis, mastocytosis prognosis, World Health Organization diagnostic criteria, management, diagnosis, retrieved articles were surveyed for additional citations. The method to adult patients with presumed mastocytosis is a diagnostic obstacle in daily practice, particularly when the doctor is unaware of the biology and etiology of the disease, no skin lesions exist, blood counts are normal and the serum tryptase level is slightly elevated or within typical range. The KIT anomaly analysis (KIT D816V) in the peripheral blood is a necessary pre-invasive test in these patients. A favorable test outcome is suggestive of the existence of SM, with all clinical consequences, including a bone marrow biopsy.**

Keywords: **Systemic mastocytosis (SM), mast cell arbitrator release signs (MCMRS), KIT anomaly analysis.**

1. INTRODUCTION

Mastocytosis is a term collectively utilized for a heterogeneous group of myeloid neoplasms defined by abnormal growth and accumulation of mast cells (MC) in one or more organ systems [(1,2,3,4)]. Depending upon the organ(s) involved, mastocytosis is divided into cutaneous mastocytosis (CM), systemic mastocytosis (SM), and localized MC tumours [(1,3,5)]. The category of the World Health Organization (WHO) includes several unique categories of CM and SM [(6,7,8)]. The clinical course and prognosis differ substantially in between such patients [(9,10)]. The clinical presentation of mastocytosis is heterogeneous, varying from skin-limited disease (cutaneous mastocytosis, CM), particularly in pediatric cases where the majority have disease-onset within the first 2 years of life and commonly experience spontaneous regression of skin lesions [(11,12,13,14)], to a more aggressive version with extra-cutaneous involvement (systemic mastocytosis, SM) that may be related to multiorgan dysfunction/failure and shortened survival, that is usually seen in adult patients [(15)].

Systemic mastocytosis (SM) constitutes a stem cell-derived clonal myeloproliferation with obvious mast cell expansion. Medical symptoms include urticaria pigmentosa and mast cell arbitrator release signs (MCMRS) such as anaphylaxis, diarrhea, and presyncope [(16)]. Other disease manifestations include osteopenia, hepatosplenomegaly, and abnormalities of blood and bone marrow. Diagnosis needs bone marrow assessment including immunohistochemical stains for mast cell tryptase or CD117 (KIT) (**Fig. 1**) [(10)]. These patients are a diagnostic challenge, particularly when the signs are non-characteristic, the physician is not knowledgeable about the possible etiology and/or the serum tryptase level is reasonably low (below 20 ng/ml). These patients might or may not suffer from an IgE-dependent allergic disease or from an atopic condition [(17,18,19)].

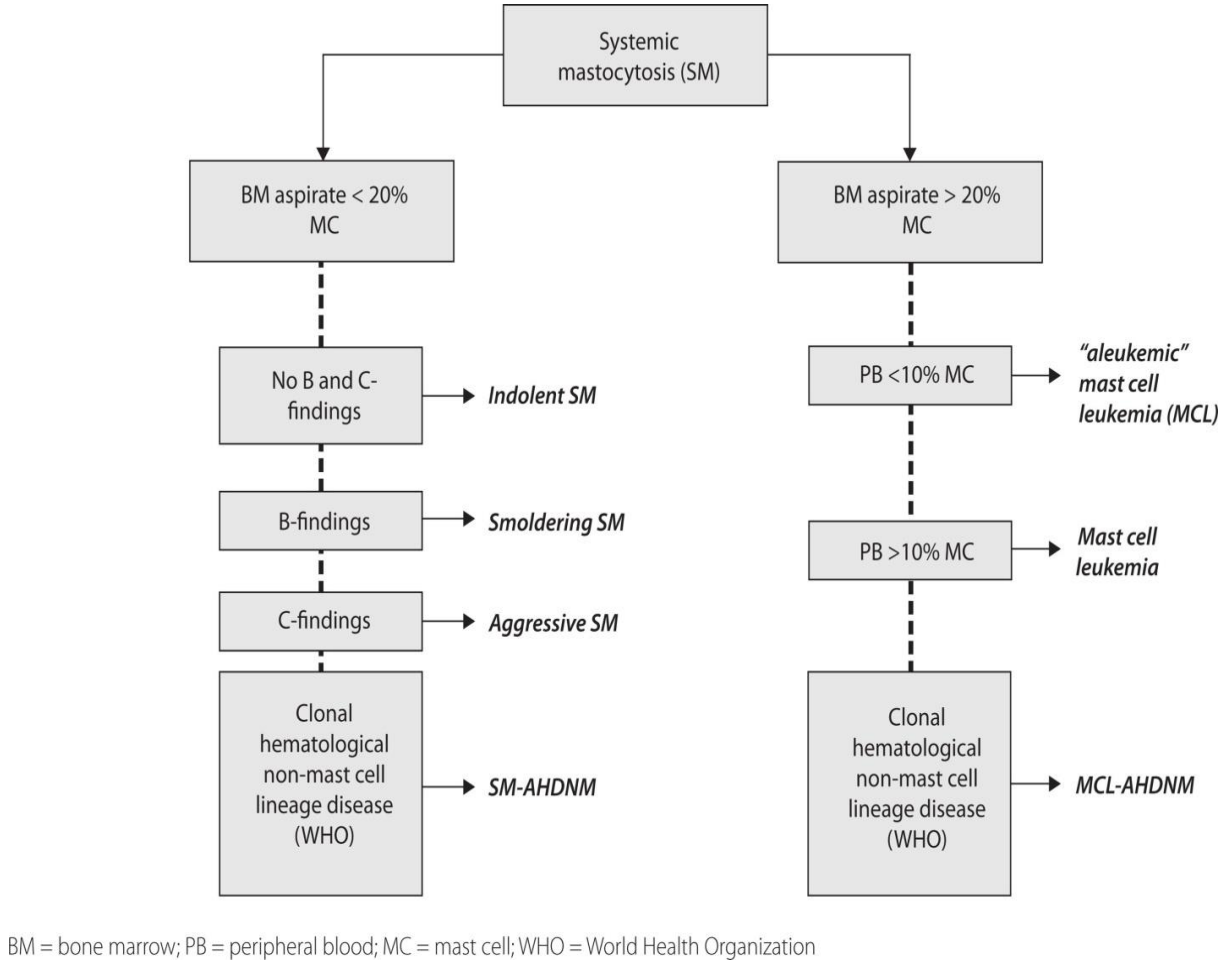

Figure 1: Diagnostic algorithm for systemic mastocytosis. [10]

This review aimed to discuss and evaluate the diagnosis approaches of Systemic mastocytosis also to be able to clear the concepts of diagnosis of this stem cell disorder, we therefore reviewed the clinical manifestations of mastocytosis.

2. METHODOLOGY

PubMed, and Embase databases searches were performed for articles published regarding diagnosis procedures of systemic mastocytosis and the diagnostic criteria and treatment options for this condition using the keywords: systemic mastocytosis, mastocytosis prognosis, World Health Organization diagnostic criteria, management, diagnosis, retrieved articles were surveyed for additional citations. Articles were reviewed for relevance to the study objectives, and more recent articles were preferentially included. and also searched the list of references of each included study for more relevant articles. We restricted our search only for human subject's articles and English language published studies, this search was up to December 2016.

3. RESULTS & DISCUSSION

✓ **Overview of mast cell:**

The mast cell originates from the pluripotent "cluster of differentiation" (CD)-34-positive haematopoietic stem cell [20]. Mast cell progenitors are known to leave the bone marrow prior to total maturation and to "house" for well-vascularized tissues. In contrast, all other myeloid cells live in the bone marrow until they have accomplished total maturation [21,22]. Murine models have caused the identification of unique mast cell progenitors and, additionally, shown that these progenitors originate from pluripotent stem cells [23]. Other studies have revealed that mast cells and basophil granulocytes are derived from a typical progenitor cell which is differentiated after the granulocyte-monocyte progenitor-stage [23]. It is possible that the order of expression of certain transcription factors, particularly up-regulation of GATA and down-

regulation of CCAAT/enhancer binding protein (C/EBP) α in the early stages, plays a crucial function in identifying the fate of the cell in respect to ending up being a basophil granulocyte or a mast cell (24).

The morphology of fully grown mast cells is really characteristic with unique granules. The cells are normally localized below or in the epithelium, close to vessels, nerves, smooth muscle cells and glandular tissue, however do not distribute in peripheral blood [22]. Mast cells for that reason act as outposts of the immune system in regards to exogenous allergens and pathogens [25]. Mast cells do not contain various kinds of granules like the neutrophil granulocyte, but various mast cell populations can consist of granules of different size and most likely various contents [26].

✓ **Classification, clinical features and prognosis of SM:**

Systemic mastocytosis was initially categorized into 'benign' and 'malignant' variations [27,28]. In 1988, Mayo Clinic investigators proposed a more intricate classifi- cation system: indolent systemic mastocytosis (ISM); systemic mastocytosis with associated hematological conditions (SM-AHD); ASM; and MCL [29]. In 2001, the WHO formalized this category and fine-tuned system (**Fig. 1**) and (**Table 1**) [10]. The WHO proposition has actually been widely embraced in scientific practice, it was not systematically verified by main information.

The signs of SM are secondary to MC conciliator release or MC seepage into affected tissues. SM is unusually detected in kids but frequently identified in grownups. The symptoms of SM are protean and nonspecific, consisting of flushing, dyspeptic stomach pain, diarrhea, frequent syncope, bone pain, and fatigue [30,31,32,33]. Gastrointestinal symptoms (**Table2**) can be worsened by spicy foods, alcohol, and tension, are chronic, and can be a reason for significant morbidity. Bone pain typically includes the pathologic fractures and long bones can happen. Constitutional symptoms, such as weight-loss, fevers, and chills, are more typical when SM exists side-by-side with a hematologic non-MC malignant neoplasm or in aggressive SM (ASM).

4 major kinds of SM are understood [10]:

1. Indolent systemic mastocytosis.

2. Systemic mastocytosis accompanied by an associated hematological non-- mast cell condition (SM-AHNMD).

3. Aggressive systemic mastocytosis and variant lymphadenopathic mastocytosis with eosinophilia.

4. Mast cell leukemia.

✓ ***Diagnosis approches of Systemic mastocytosis:***

More just recently, diagnostic standards, algorithms, and recommendations to assist in execution of the WHO requirements (**Table 1**) have been proposed and initial descriptions of new provisionary subvariants have actually been described; [34,35,36,37,38,39] these include well-differentiated systemic mastocytosis [40,41] and clonal mast cell-activation syndromes in the lack of skin sores, likewise described as monoclonal mast cell-activation syndrome [40] or clonal mast cell-activation disorders, [10] the later on only partly fulfilling the requirements for systemic mastocytosis [10, 41].

Table 1: Criteria for systemic mastocytosis[a] Diagnosis requires 1 major and 1 minor criterion or 3 minor criteria [10]
Major:
Multifocal dense infiltrates of mast cells in tissue sections[b]
Minor:
>25% spindled, immature or atypical mast cells in tissue sections or bone marrow aspirate smears
Detection of KIT D816 V mutation Expression of CD2 and/or CD25 in mast cells Serum total tryptase persistently exceeds 20 ng/mL[c]

[a] 2008 World Health Organization Diagnostic Criteria for Systemic Mastocytosis.

[b] Infiltrate is 15 mast cells in aggregates in bone marrow and/or extracutaneous organs.

[c] Not valid if there is an associated clonal myeloid disorder.

Indolent systemic mastocytosis involves skin and bone marrow and is the most typical kind of SM. Variants of indolent SM include bone marrow mastocytosis, where no skin disease exists, smoldering systemic mastocytosis where 2 or more "B findings" are present (**Table 2**) [10], and well-differentiated (round cell) mastocytosis, talked about later on. Smoldering

SM generally impacts older patients and is associated with more constitutional symptoms than the other types of indolent disease. In systemic mastocytosis accompanied by an associated hematological non-- mast cell condition (SM-AHNMD), the associated non-- mast cell condition is typically a myeloid malignancy, however might also include lymphomas or plasma cell neoplasms. Symptoms and diagnosis typically reflect the associated non- mast cell disease. Aggressive systemic mastocytosis is a condition usually lacking skin sores and providing with several "C findings" that indicate organ dysfunction owing to mast cell infiltration (**Table 2**) [10,41]. A variant of aggressive SM is lymphadenopathic mastocytosis with eosinophilia, which presents with lymphadenopathy and eosinophilia [40,41].

Table 2: "B Findings" and "C Findings" used to subcategorize systemic mastocytosis
B Findings
1. Increased mast cell burden: >30% mast cell aggregates on bone marrow biopsy and/or total serum tryptase level >200 ng/mL
2. Dysplasia or myeloproliferation: Hypercellular marrow, signs of myelodysplasia or abnormal myeloid proliferation, and normal or slightly abnormal blood counts, without sufficient criteria to diagnose an AHNMD
3. Organomegaly: Palpable hepatomegaly without ascites or signs of liver dysfunction, palpable or radiologic lymphadenopathy (>2 cm), or palpable splenomegaly, without hypersplenism
C Findings
1. Cytopenias: ANC <1.0 10^9/L; Hb <10 g/dL; or platelets <100 10^9/L
2. Liver: Palpable hepatomegaly with impaired liver function, ascites, and/or portal hypertension
3. Bone: Large osteolytic lesions and/or pathologic fractures
4. Spleen: Palpable splenomegaly with hypersplenism
5. Gastrointestinal: Malabsorption with weight loss and/or hypoalbuminemia

Bone marrow histology as a diagnostic procedure for SM:

In practice, the current diagnostic method for SM starts with a BM assessment given that this site is nearly widely included in adult mastocytosis, and histological diagnostic criteria for non-BM, extracutaneous organ involvement in SM have not been securely established or widely accepted as of. Even more, BM assessment also permits detection of a 2nd hematologic neoplasm, if present [28,29]. In general, the pathognomonic multifocal dense MC aggregates, often in paratrabecular and/or perivascular BM locations (significant diagnostic requirement), may not be readily acknowledged by basic dyes such as Giemsa, particularly when MC show significant hypogranulation or irregular nuclear morphology, or in cases with substantial BM involvement by a 2nd hematological neoplasm (e.g., acute myeloid leukemia), or when substantial reticulin fibrosis exists. Among the immunohistochemical markers, tryptase is the most sensitive, given that practically all MC, irrespective of their phase of maturation, activation status, or tissue of localization express this marker, and subsequently permits detection of even small and/or immature MC infiltrates [34,42,43]. It needs to be stressed however that neither tryptase nor KIT/CD117 immunostaining has the ability to compare neoplastic and normal MC [44]. Abnormal basophils seen in some cases of chronic and acute basophilic leukemia, as well as in chronic myeloid leukemia (CML), and blasts in some AML cases may be tryptase favorable, and might show challenging to differentiate from MC [29]. On the other hand, immunohistochemical detection of aberrant CD25 expression on bone marrow MC appears to be a dependable diagnostic tool in SM, provided its ability to discover irregular MC in all SM subtypes, consisting of the uncommon cases with a loosely spread, interstitial pattern of MC participation [43].

Diagnosis of SM using Mast cell immunophenotyping:

Neoplastic MC generally express CD25 and/or CD2, and the abnormal expression of at least one of these 2 antigens counts as a minor criterion toward the diagnosis of SM per the WHO system [45]. Expression of CD2 on MC, as assessed by either circulation cytometry or immunostaining, has been kept in mind to be variable in SM, and consequently, CD25 expression may be more dependable marker for neoplastic MC [46,47]. The aforementioned immunostaining and immunophenotyping studies improve the morphological and immunophenotypic difference between normal (round and CD25-negative) and irregular (spindle-shaped and CD25-positive) mast cells, respectively [47].

Diagnosis of SM using Serum tryptase level:

Normal MC display a spectrum of "activation levels" *in vivo*, and the mechanisms governing the secretory phenotype and mediator release patterns are not completely understood (48). In SM, an elevated serum tryptase level (>20 ng mL^{-1})

counts as a minor diagnostic criterion per the WHO framework (45); while the levels vary widely, serum tryptase is elevated in the vast majority of SM patients across all WHO subgroups; a significantly greater proportion of ASM and SM-AHNMD patients exhibit a markedly elevated serum tryptase level (>200 ng/mL) compared to those with ISM (15). Serum tryptase levels are also elevated in a significant proportion of cases with AML, CML, and MDS (49); consequently, this test has limited diagnostic utility in the presence of a second SM-associated myeloid neoplasm. The correlation between MC mediator levels and presence of MC mediator-release symptoms (MCMRS) or systemic MC burden remains incompletely understood; in one study of indolent mastocytosis patients, MC mediator levels were significantly correlated with BM MC burden, but not MCMRS (49).

4. CONCLUSION

The method to adult patients with presumed mastocytosis is a diagnostic obstacle in daily practice, particularly when the doctor is unaware of the biology and etiology of the disease, no skin lesions exist, blood counts are normal and the serum tryptase level is slightly elevated or within typical range. The KIT anomaly analysis (KIT D816V) in the peripheral blood is a necessary pre-invasive test in these patients. A favorable test outcome is suggestive of the existence of SM, with all clinical consequences, including a bone marrow biopsy.

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