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A Comprehensive Review of Mastocytosis From Pathophysiology to Management Strategies

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Abstract:

Introduction: Mastocytosis is a rare hematologic neoplasm characterized by the abnormal proliferation and accumulation of mast cells in various tissues. Its clinical manifestations vary widely, ranging from cutaneous lesions to systemic involvement with potentially life-threatening symptoms. Understanding the pathophysiology, diagnosis, and management of mastocytosis is crucial for improving patient outcomes.

Aim of the Study: The aim of this study was to provide a comprehensive overview of mastocytosis, including its epidemiology, risk factors, pathophysiology, clinical manifestations, diagnostic approaches, and management strategies. By synthesizing current knowledge on mastocytosis, this study aims to enhance understanding of the disease and guide clinical practice.

Description of the State of Knowledge: Mastocytosis is classified into cutaneous and systemic forms, with various subtypes based on clinical and histopathological features. Diagnosis relies on a combination of clinical suspicion, serum tryptase levels, histological examination of bone marrow biopsies, and genetic testing. Management strategies include symptomatic treatment, avoidance of triggers, and targeted therapies such as monoclonal antibodies and

tyrosine kinase inhibitors. Advanced forms may require cytoreductive therapy or allogeneic hematopoietic stem cell transplantation (alloHSCT).

Conclusions: Despite advancements in diagnosis and treatment, achieving lasting remission in mastocytosis remains challenging, especially in advanced cases. Further research into the molecular mechanisms underlying the disease and the development of novel therapeutic modalities are needed to improve patient outcomes and quality of life.

Keywords: Mastocytosis, Mast cells, Pathophysiology, Diagnosis, Management, Treatment

Introduction

Mastocytosis is a rare and clinically heterogeneous clonal hematologic neoplasm that is characterized by the expansion and accumulation of clonal tissue mast cells in various organs, including the skin [1].

Mast cells play a significant role in health and disease, particularly in conditions such as atopic dermatitis, contact hypersensitivity reactions, and wound healing [2]. They are involved in defense against pathogens, allergic responses, and anaphylaxis, and can also recruit other immune cells and modulate the immune response [3]. In mastocytosis, the elevation of mast cell mediators, particularly serum tryptase, is a key diagnostic criterion, and relief of symptoms can be achieved by inhibiting these mediators [4]. However, the functional significance of mast cells in delayed type hypersensitivity and their role in some diseases, such as cancer and autoimmune inflammation, remain unclear [3]

The disease was first described in 1869 by Nettleship et al. and That year, it was identified as a disorder with multiple clinicopathological diversity. There are two basic forms of mastocytosis: cutaneous mastocytosis (CM) - pertains to the skin and systemic mastocytosis exclusively, which involves extracutaneous tissues (e.g. liver, spleen, bone marrow and lymph nodes) [5]

The classification of mastocytosis has evolved as diagnostic criteria and understanding have advanced. The classification by the World Health Organization (WHO) of myeloid cancers was revised in 2016 [1]. According to the latest WHO classification, mastocytosis is divided into: cutaneous mastocytosis, systemic mastocytosis and mast cell sarcoma, while systemic mastocytosis is in turn divided into: indolent SM, smoldering SM, aggressive SM, bone marrow SM, SM with an associated hematologic neoplasm and mast cell leukemia [6].

Table 1. Classification of mastocytosis according to WHO

Cutaneous mastocytosis (CM)	Systematic mastocytosis (SM)	Mast cell sarcoma
<ul style="list-style-type: none"> - maculopapular CM (MPCM) - diffuse CM (DCM) - mastocytoma 	<ul style="list-style-type: none"> - bone marrow mastocytosis (BMM) - indolent SM (ISM) - smoldering SM (SSM) - SM with an associated hematologic neoplasm (SM-AHN) - aggressive SM (ASM) - mast cell leukemia (MCL) 	

Epidemiology and Risk Factors

The incidence of mastocytosis is estimated to be approximately 10 per 100,000 people, with incidence rates across different regions range from 0.77 to 2.77 per 100,000 person-years.[7]

The most common variant of this disease in adults is slow systemic mastocytosis (ISM), its incidence is estimated at 13 per 100,000 inhabitants. The occurrence of this disease is increasingly observed in society, which may be due to greater awareness and improved diagnostic methods.[8]

Mastocytosis can manifest in individuals of all ages, spanning from childhood to adulthood. Among adults, the condition shows no particular age bias, although mortality rates tend to be higher in older individuals. [9] In contrast, in children, mastocytosis predominantly affects boys, and symptoms typically emerge within the initial year of life. [10] Regarding systemic mastocytosis, the average age at which it is diagnosed is approximately 52.4 years, with a slightly elevated occurrence in females [11].

Factors that increase the risk of mastocytosis and its associated complications, including anaphylaxis and a poorer prognosis, include genetic predisposition, notably mutations in the KIT receptor, older age, anemia, thrombocytopenia, genetic mutations, atopic tendencies, and specific clinical and laboratory characteristics. While there is some indication of a link between mastocytosis and malignant melanoma, additional research is required to clarify this potential association. [12,13]

Pathophysiology of Mastocytosis

The pathophysiology of mastocytosis revolves around the dysregulation of mast cell growth and function. Ordinarily, mast cells originate from precursor cells in the bone marrow known as mast cell progenitors. These progenitors develop into mature mast cells under the influence of various growth factors and cytokines. In mastocytosis, there is an abnormal proliferation of identical mast cells originating from a single mutated mast cell. The majority of mastocytosis cases are linked to mutations in the KIT gene, responsible for encoding the receptor for a growth factor called stem cell factor (SCF). Mutations in KIT result in the continuous activation of the receptor, leading to uncontrolled growth and survival of mast cells. The most common mutations occur in exon 17 of the KIT gene, particularly the D816V mutation, although other mutations can also arise.

The excessive accumulation of mast cells in tissues leads to the hallmark symptoms of mastocytosis. In cutaneous mastocytosis, affecting primarily the skin, mast cells build up in the dermis and/or epidermis, causing the formation of pathological lesions. In systemic

mastocytosis, mast cells can infiltrate various organs and tissues throughout the body, including the bone marrow, spleen, liver, gastrointestinal tract, and lymph nodes.

Mast cell activation in mastocytosis can be triggered by various stimuli such as physical pressure, temperature changes, medications, insect stings, and specific foods. Upon activation, mast cells release stored granules containing numerous inflammatory mediators like histamine, tryptase, prostaglandins, leukotrienes, and cytokines. These mediators exert both local and systemic effects, contributing to the diverse range of symptoms associated with mastocytosis.

[14.15]

Clinical Manifestations

Cutaneous Mastocytosis: Subtypes, Clinical Features

There are three subtypes of cutaneous mastocytosis: maculopapular CM, diffuse CM, mastocytoma. Clinical presentations may differ based on the subtype and severity of the condition, but typical indications encompass:

- Skin anomalies: Initially, these may manifest as small, reddish-brown or yellow-brown spots or patches on the skin, varying in shape from flat to raised and ranging from a few millimeters to several centimeters in diameter.
- Itching (Pruritus): Itching, also referred to as pruritus, is a prevalent symptom of cutaneous mastocytosis, ranging from mild to severe and potentially triggered by factors such as heat, friction, stress, or exposure to specific substances like hot water or spicy foods.
- Redness: Individuals with cutaneous mastocytosis may experience skin flushing, particularly following exposure to triggers such as heat, stress, certain foods, or medications. The redness may be transient or persistent and can vary in severity
- Darier's sign: This sign, characteristic of mastocytosis, involves rubbing or stroking a skin lesion, resulting in its elevation, redness, and itching due to histamine release from mast cells.
- Blisters: In certain instances, cutaneous mastocytosis may lead to the formation of blisters (vesicles) on the skin. These blisters may contain clear fluid (vesicles) or blood (hemorrhagic blisters) and may cause discomfort or itching. [16.17,18]

Systemic Mastocytosis: Variants, Organ Involvement, and Symptomatology

There are a few subtypes of systemic mastocytosis: bone marrow mastocytosis (BMM), indolent SM (ISM), smoldering SM (SSM), SM with an associated hematologic neoplasm (SM-AHN), aggressive SM (ASM), mast cell leukemia (MCL).[20]

Indolent systemic mastocytosis (ISM): This is the most common form of systemic mastocytosis, characterized by slow disease progression and relatively mild symptoms. Patients with ISM usually have a normal life expectancy and may experience occasional episodes of symptoms such as skin redness, itching, abdominal pain, and fatigue.

Smoldering systemic mastocytosis (SSM): SSM is similar to ISM, but tends to have a slightly more aggressive disease course. Patients with SSM may experience more frequent or more severe symptoms, as well as involvement of organs outside the skin. [20]

Systemic mastocytosis with associated hematologic malignancy (SM-AHN): In this variant, patients have both systemic mastocytosis and another hematologic disorder such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN). This combination of disorders can complicate diagnosis and treatment. [20,21]

Aggressive systemic mastocytosis (ASM): ASM is a rare and more severe form of systemic mastocytosis characterized by rapid disease progression and organ damage. Patients with ASM may experience symptoms such as organ enlargement, low blood cell counts, weight loss and debilitating fatigue. This variant requires rapid medical intervention and aggressive treatment. [20,21]

Mast cell leukemia (MCL): MCL is the most aggressive and life-threatening form of systemic mastocytosis. It is characterized by the presence of large numbers of malignant mast cells circulating in the bloodstream. Patients with MCL often experience severe symptoms such as organ failure, severe anemia, and a high risk of infection. Treatment options for MCL are limited and the prognosis is poor. Systemic mastocytosis can affect various organs and tissues throughout the body, leading to a variety of symptoms. [20,21]

Common symptoms of the disease include: [20]

- Gastrointestinal symptoms: Patients may experience abdominal pain, diarrhea, nausea, vomiting and gastrointestinal bleeding due to mast cell infiltration in the gastrointestinal tract.

- Cardiovascular symptoms: Palpitations, low blood pressure (hypotension), and syncope (syncope) may occur due to the release of mediators such as histamine, which can affect blood vessel function.
- Respiratory symptoms: may include wheezing, shortness of breath, coughing and difficulty breathing, especially when mast cells spread to the lungs.
- Neurologic symptoms: Headaches, dizziness, cognitive impairment, and mood changes may occur, although these symptoms are less common than others.
- Bone and joint symptoms: Bone pain, fractures and osteoporosis may occur due to mast cell infiltration in the bone marrow and bone tissue.

Associated Conditions: Anaphylaxis

Symptoms in patients with mastocytosis result from excessive release of mediators from mast cells, either spontaneously or in response to triggers such as temperature changes, physical activity, insect stings, alcohol, infections, NSAIDs, and emotional stress. The manifestation of symptoms varies greatly among individual patients, ranging from isolated symptoms to life-threatening anaphylactic reactions resembling anaphylactic shock, characterized by a sudden feeling of heat, palpitations, dizziness and drop in blood pressure leading to fainting. After such episodes, patients often experience profound fatigue lasting up to 24 hours. Studies have shown a significant association between mastocytosis and anaphylaxis, with the incidence of anaphylaxis in adults with mastocytosis being approximately 1,000 times higher than in the general population. Therefore, patients who experience severe or recurrent anaphylaxis should be evaluated for mastocytosis by assessing baseline serum tryptase levels. [21,22]

Diagnostic Approaches

Clinical suspicion of mastocytosis usually begins with the recognition of signs and symptoms related to the release of mast cell (MC) mediators or the recognition of characteristic skin lesions. However, it is not possible to diagnose mastocytosis based solely on symptoms. The initial step involves assessing serum tryptase levels. In most patients with mastocytosis, these levels are higher than normal, reflecting overall mast cell loading and activation. However, elevated tryptase levels are not the sole cause of mastocytosis; may also occur in other

conditions such as acute or chronic myeloid leukemia and myeloproliferative disorders, so it is only a guide.[21]

According to the World Health Organization diagnostic guidelines, there are detailed criteria for diagnosing mastocytosis: one major criterion and four minor criteria. A diagnosis of mastocytosis can be made when one major and one minor criterion are met, or when three minor criteria are met.[23]

Table 2. Diagnostic criteria for mastocytosis

Major criterion	Minor criteria
1. Multifocal MCs aggregates (>15 mast cells per cluster) in biopsy sections of bone marrow and/or other extracutaneous organ(s)	1. In biopsy sections, >25% of the MCs (CD117+) in the infiltrate are spindle-shaped or have atypical morphology 2. Detection of codon 816 c-kit mutation in bone marrow, blood or other extracutaneous organ(s) 3. Detection of aberrant MC clones coexpressing CD117 with CD2 and/or CD25 in bone marrow or blood or another extracutaneous organ(s) 4. Baseline serum tryptase persistently exceeds 20 ng mL ⁻¹ (in the case of an unrelated myeloid neoplasm)

A crucial aspect of diagnosing mastocytosis involves conducting a bone marrow biopsy and assessing it. The primary diagnostic criterion for this condition is identifying at least 15 multifocal dense mast cell infiltrates in the bone marrow or other organs beyond the skin. Additional indicators include: observing more than 25% of mast cells (CD117+) in the infiltrate exhibiting spindle-shaped or abnormal morphology, finding the c-kit mutation at codon 816 in the bone marrow, blood, or other organs, and identifying aberrant mast cell clones that coexpress CD117 with CD2 and/or CD25 in the bone marrow, blood, or other

organs. However, meeting the main histological criterion can be challenging as only small clusters or scattered mast cells may be visible in the bone marrow. In such instances, supplementary tests such as flow cytometry are necessary for confirming systemic mastocytosis, as they may reveal abnormal findings.[21,23]

After confirming a diagnosis of MS, a sequence of staging examinations is necessary. These include chest, abdomen, and pelvis CT scans, scintigraphy or skeletal assessments, and bone density tests, to determine the specific subtype of the condition.[21]

Genetic testing is another key step in the diagnosis of mastocytosis. Research focuses on identifying genetic biomarkers and mutations associated with the disease. The KIT D816V mutation is a recurrent genetic alteration found in mastocytosis, and its sensitive detection, along with next-generation sequencing (NGS) to profile additional mutations, is crucial in the diagnosis and prognosis of systemic mastocytosis (MS). Examining the patient's genetic profile, especially identifying somatic mutations such as TET2, SRSF2, ASXL1, RUNX1, CBL and JAK2, is important for understanding the clinical and cellular phenotypes of advanced systemic mastocytosis, as it has been shown that the occurrence of these mutations may precede the appearance of mutations. KIT D1816V, therefore detecting these mutations earlier may be important in terms of diagnosis and treatment selection.[24]

Additionally, an essential diagnostic tool is tryptase immunostaining, because this test is very sensitive in detecting fat cell infiltration, especially in the case of malignant variants of this disease, so it is worth remembering about the possibility of using this test.[25]

Management Strategies

There are various treatment strategies for mastocytosis. We distinguish aspects of treatment consisting in symptomatic treatment, avoidance of risk factors and targeted therapies based on detected genetic and bone marrow abnormalities. Symptomatic treatment may include the use of antihistamines to reduce itching, redness, and gastrointestinal symptoms. It may also be possible to prescribe medications such as leukotriene inhibitors and mast cell stabilizers to prevent mast cells from activating and releasing inflammatory chemicals. Avoiding risk factors is important due to the possibility of causing an anaphylactic reaction, including: certain foods (such as alcohol, shellfish and foods high in histamine), medications (such as

nonsteroidal anti-inflammatory drugs and some antibiotics), insect stings, stress and extreme temperatures.[26-28]

The treatment also uses monoclonal antibodies, including omalizumab, which binds to IgE, it is not a curative therapy, but it can be used in patients resistant to treatment, it reduces the severity of symptoms related to the action of mast cells accumulated in the body, and also limits the occurrence of episodes anaphylaxis.[21,29]

The most important therapy is the use of tyrosine kinase inhibitors, as they target the KIT mutation, which disrupt the proliferation and shorten the survival time of mast cells. Various therapeutic strategies are being developed based on molecular diagnostics, such as cytoreductive therapy and targeted therapies. However, they are currently indicated only in advanced forms of mastocytosis. The most commonly used drugs include interferon (INF)- α and cladribine. Interferon- α is a first-line drug, it is used together with prednisone in a combined form, its actions are based on alleviating the symptoms of mast cell regeneration and reducing the infiltration in the bone marrow. Cladribine, in turn, is used in the next line in patients who are found to be resistant to first-line therapy. However, these drugs are significantly toxic and this should be remembered.[21,30]

Despite the development of treatment options, available pharmacological agents do not ensure lasting remission of the disease, especially in patients with advanced mastocytosis. Only alloHSCT has the potential to cure the patient and this therapeutic option should be considered in patients.[27]

Conclusion

In conclusion, mastocytosis presents a complex spectrum of clinical manifestations stemming from the dysregulation of mast cell growth and function. The classification of this condition has evolved over time, with the latest WHO classification delineating various subtypes based on clinical and histopathological features. Despite being a rare disorder, the incidence of mastocytosis appears to be increasing, possibly due to heightened awareness and improved diagnostic techniques. Risk factors for mastocytosis include genetic predisposition, specific

mutations such as those in the KIT gene, and certain clinical and laboratory characteristics. Diagnosis relies on a combination of clinical suspicion, serum tryptase levels, histological examination of bone marrow biopsies, and genetic testing. Treatment strategies encompass symptomatic management, avoidance of triggers, and targeted therapies aimed at the underlying genetic and bone marrow abnormalities. Monoclonal antibodies and tyrosine kinase inhibitors show promise in alleviating symptoms and targeting the mutated KIT receptor. However, advanced forms of mastocytosis may require cytoreductive therapy or even alloHSCT for potential cure. Despite therapeutic advancements, achieving lasting remission remains a challenge, especially in advanced cases. Further research into the molecular mechanisms underlying mastocytosis and the development of novel therapeutic modalities are warranted to improve patient outcomes and quality of life.

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