QUALITY IN SPORT
eISSN 2450-3118 · Open Access · Peer-reviewed
apcz.umk.pl/QS Nicolaus Copernicus University in Toruń

Cite as: KOZŁOWSKA, Alicja, PRZYBYSZ, Karolina, STADNIK, Luiza, ZIENKIEWICZ , Natalia, RACHOŃ, Jarosław, DZWONKOWSKA, Adela, DZWONKOWSKI, Jakub, TROCKA, Daria, WORONIECKA, Natalia and SZERENOS, Nicol. Mastocytosis: Pathophysiology, Clinical Manifestations, and Current Therapeutic Approaches – A Narrative Review. Quality in Sport. 2026;61:73022. https://doi.org/10.12775/QS.2026.61.73022

ARTICLE TIMELINE
Received: 03.06.2026. Revised: 03.07.2026. Accepted: 04.07.2026. Published: 08.07.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

Mastocytosis: Pathophysiology, Clinical Manifestations, and Current Therapeutic Approaches – A Narrative Review

Alicja Kozłowska (AK), ORCID https://orcid.org/0009-0000-5991-7401

E-mail alicja.kozlowska23@gmail.com

Szpital Morski im. PCK: Gdynia, Poland

Karolina Przybysz (KP), ORCID https://orcid.org/0009-0002-9001-829X

E-mail karola1003@gmail.com

Szpital Morski im. PCK: Gdynia, Poland

Luiza Stadnik (LS), ORCID https://orcid.org/0009-0009-6854-4905

E-mail luizamstadnik@gmail.com

Szpital św. Wojciecha Copernicus PL Sp. z o.o.: Gdańsk, Poland

Natalia Zienkiewicz (NZ), ORCID https://orcid.org/0009-0009-3380-0470

E-mail nataliazienkiewicz21@gmail.com

Szpital Morski im. PCK: Gdynia, Poland

Jarosław Rachoń (JR), ORCID https://orcid.org/0009-0007-9691-2221

E-mail jaroslaw.rachon@gmail.com

Uniwersyteckie Centrum Kliniczne, Gdańsk, Poland

Adela Dzwonkowska (AD), ORCID https://orcid.org/0009-0004-7026-7437

E-mail adelaziolkowska@gmail.com

Szpitale Tczewskie S.A., Tczew, Poland

Jakub Dzwonkowski (JD), ORCID https://orcid.org/0009-0006-5087-0698

E-mail jakub.dzwonk@gmail.com

Szpital Wojewódzki im. Mikołaja Kopernika, Koszalin, Poland

Daria Trocka (DT), ORCID https://orcid.org/0000-0001-9684-5881

E-mail dariatrocka99@gmail.com

Szpital św. Wojciecha w Gdańsku, Gdańsk, Poland

Natalia Woroniecka (NW), ORCID https://orcid.org/0009-0006-4713-4526

E-mail nworoniecka@op.pl

Samodzielny Publiczny Zakład Opieki Zdrowotnej MSWiA w Gdańsku, Poland

Nicol Szerenos (NS), ORCID https://orcid.org/0009-0009-2754-8344

E-mail nicolszerenos@gmail.com

Szpital Morski im. PCK: Gdynia, Poland

Corresponding Author

Alicja Kozłowska, E-mail alicja.kozlowska23@gmail.com

Abstract

Background. Mastocytosis is a heterogeneous group of clonal mast cell disorders characterized by abnormal mast cell accumulation and activation in the skin, bone marrow, and other organs. Recent advances in molecular diagnostics and targeted therapies have significantly improved understanding of disease biology and management.

Aim. This review aims to summarize current knowledge regarding the classification, pathophysiology, clinical manifestations, diagnosis, treatment, and prognosis of mastocytosis.

Material and methods. A narrative review was performed by searching PubMed, Google Scholar, Scopus, and Medline for English-language articles. Precedence was given to current literature, clinical research, and international recommendations. Search terms included mastocytosis, systemic mastocytosis (SM), cutaneous mastocytosis (CM), mast cell, and KIT mutation.

Results. Mastocytosis is classified into cutaneous mastocytosis, systemic mastocytosis, and mast cell sarcoma. Disease pathogenesis is primarily associated with activating KIT mutations,

particularly KIT D816V, together with additional somatic mutations and microenvironmental factors contributing to disease heterogeneity and progression. Clinical manifestations result from mast cell mediator release and tissue infiltration. Diagnosis requires integration of clinical, histopathological, immunophenotypic, and molecular findings. Treatment strategies range from anti-mediator therapy in indolent disease to KIT-targeted therapies, including midostaurin and avapritinib, in advanced systemic mastocytosis.

Conclusions. Mastocytosis remains a clinically diverse disorder requiring multidisciplinary diagnostic and therapeutic approaches. Advances in molecular characterization and targeted treatment have improved prognostic assessment and expanded therapeutic options, particularly in advanced disease.

Key words: mastocytosis, systematic mastocytosis, cutaneous mastocytosis, mast cell, KIT mutation

1. Introduction

Mastocytosis is a rare and heterogeneous group of disorders characterized by the clonal proliferation and accumulation of abnormal mast cells in one or more organs, most commonly the skin and bone marrow [1,2]. In adults, the disease typically presents as systemic mastocytosis, whereas pediatric cases are more often limited to cutaneous involvement [2,3]. According to current classification systems, mastocytosis is broadly divided into cutaneous mastocytosis and systemic mastocytosis, with the latter encompassing a spectrum ranging from indolent disease to aggressive variants associated with organ dysfunction and reduced survival [4].

The pathogenesis of mastocytosis is closely associated with constitutive activation of the KIT receptor tyrosine kinase, most frequently due to the KIT D816V mutation, which is detected in the majority of adult patients with systemic mastocytosis [5]. This mutation leads to uncontrolled mast cell proliferation, survival, and accumulation in tissues [5]. In addition to clonal expansion, mast cell activation and excessive release of bioactive mediators such as histamine, tryptase, prostaglandins, leukotrienes, and cytokines play a central role in disease pathophysiology [6].

The clinical presentation of mastocytosis is highly variable and reflects both mediator-related effects and organ infiltration by mast cells. Patients may present with dermatologic,

gastrointestinal, cardiovascular, and systemic symptoms, including pruritus, flushing, abdominal pain, diarrhea, hypotension, and anaphylaxis [7,8]. This broad and often nonspecific symptom profile frequently contributes to delayed diagnosis and misinterpretation as allergic or functional disorders [8].

Recent advances in molecular diagnostics and targeted therapies have significantly improved the understanding and management of mastocytosis [9,10]. In particular, the development of KIT-targeted agents has introduced new therapeutic possibilities and improved clinical outcomes in selected patient populations [10].

The aim of this narrative review is to synthesize current evidence on mastocytosis, with a particular focus on its clinical manifestations and contemporary therapeutic approaches, in order to provide a comprehensive and clinically relevant overview of this complex and heterogeneous disease.

2. Research materials and methods

This study was conducted as a narrative literature review aimed at synthesizing current scientific evidence regarding the pathophysiology, clinical manifestations, diagnosis, and management of mastocytosis. Scientific publications indexed in the PubMed, Scopus, Google Scholar, Medline databases were analyzed. The search strategy included combinations of the following keywords: “mastocytosis”, “systemic mastocytosis”, “cutaneous mastocytosis”, “mast cells”, “KIT mutation”. To write this review article, 37 articles were analyzed. Only articles published in English and relevant to the topic were included. Priority was given to recent reviews, clinical studies, and international guidelines.

2.1 Declaration on the Use of Artificial Intelligence

AI-assisted tools were used exclusively for linguistic refinement and structural editing of the manuscript. The authors have reviewed and edited the content as needed and take full responsibility for the scientific content, interpretation of the data, and final version of the manuscript.

3. Research results

3.1. Classification

The most recent classification of mastocytosis was established in both the 2022 International Consensus Classification (ICC) and the 5th edition of the WHO classification of haematolymphoid tumours [11,12]. These frameworks currently constitute the standard reference for diagnosis, prognostic stratification, and clinical management.

Both systems categorize mastocytosis into three principal entities: cutaneous mastocytosis (CM), characterized by disease confined to the skin, predominantly affecting children and generally associated with a favorable clinical course; systemic mastocytosis (SM), defined by involvement of one or more extracutaneous organs, more commonly observed in adults and typically associated with a less favorable prognosis; and mast cell sarcoma (MCS), a rare, localized, and highly aggressive mast cell neoplasm [13].

Table 1. Comparison between the two classifications:

International Consensus Classification (ICC) mastocytosis subtypes (variants)	World Health Organization 5th Edition classification of mastocytosis
Cutaneous mastocytosis:	
Urticaria pigmentosa/maculopapular cutaneous mastocytosis	Urticaria pigmentosa/maculopapular cutaneous mastocytosis • Monomorphic • Polymorphic
Diffuse cutaneous mastocytosis	Diffuse cutaneous mastocytosis
Mastocytoma of skin	Cutaneous mastocytoma • Isolated mastocytoma

	• Multilocalized mastocytoma
Systemic mastocytosis:	
Smoldering systemic mastocytosis	Smoldering systemic mastocytosis
Aggressive systemic mastocytosis	Aggressive systemic mastocytosis
Systemic mastocytosis with an associated myeloid neoplasm	Systemic mastocytosis with an associated hematologic neoplasm
Mast cell leukemia	Mast cell leukemia
Indolent systemic mastocytosis (includes bone marrow mastocytosis)	Bone marrow mastocytosis
	Indolent systemic mastocytosis
Mast cell sarcoma	
no further subclassification of mast cell sarcoma	

These classifications reflect the extent of organ involvement and the biological behavior of the disease.

3.2. Pathophysiology

Mast cells (MCs) are tissue-resident immune cells that play a central role in both innate and adaptive immunity, particularly in allergic and inflammatory responses [14]. MCs originate from multipotent hematopoietic stem cells (HSCs) in the bone marrow, progressing through common myeloid and granulocyte–monocyte progenitors [15]. Unlike most hematopoietic cells, mast cells are released into the circulation as immature precursors and subsequently migrate to peripheral tissues, such as the skin and mucosa, where they undergo terminal differentiation [16]. The development, survival, and functional activation of MCs are

critically dependent on stem cell factor (SCF), the ligand for the KIT receptor (CD117), which regulates mast cell maturation, proliferation, and degranulation at all stages of development [16, 17]. Additional cytokines, including interleukins IL-3, IL-4, IL-6, IL-9, and IL-13, may contribute to mast cell growth and differentiation; however, their role is considered supportive rather than essential compared to SCF signaling [16].

The majority of patients with cutaneous as well as systemic forms of mastocytosis harbor somatic point mutations in the KIT gene within neoplastic mast cells [5, 16]. These gain-of-function mutations result in constitutive activation of the KIT receptor, leading to ligand-independent signaling and uncontrolled mast cell proliferation [18]. The most prevalent mutation in adult systemic mastocytosis is KIT D816V in exon 17, detected in over 90% of cases [19]. In contrast, this mutation is less frequently observed in childhood-onset disease, being present in up to 30% of cutaneous mastocytosis cases [20].

The presence of KIT D816V alone does not fully explain disease pathogenesis, as it is also detected in patients with indolent systemic mastocytosis without clear correlation to symptom severity. Furthermore, emerging evidence indicates that KIT D816V may appear relatively late in disease pathogenesis, indicating that additional genetic alterations may precede and contribute to clonal evolution [20].

Beyond activating KIT mutations, the pathogenesis of mastocytosis is increasingly understood as a multistep process involving additional somatic mutations and inherited modifiers. In advanced systemic mastocytosis, most patients acquire two or more additional somatic mutations beyond KIT, whereas those lacking such mutations tend to have a less aggressive clinical course and longer overall survival [21]. That might suggest that while KIT mutations are critical for mast cell expansion and survival, additional genetic alterations likely promote malignant progression. A substantial proportion of patients with advanced systemic disease harbor mutations in genes commonly associated with other myeloid neoplasms. These include alterations in epigenetic regulators (e.g., TET2, ASXL1, DNMT3A, EZH2), splicing factors (SRSF2, SF3B1, U2AF1), transcription factors (RUNX1), and components of signaling pathways (JAK2, NRAS, KRAS, CBL) [22, 23]. Among these, mutations in SRSF2, ASXL1, and RUNX1 (the “S/A/R” gene panel) are strongly associated with adverse prognosis, increased disease aggressiveness, and reduced overall survival [24]. In addition to somatic mutations, disease pathogenesis is influenced by permissive genetic and microenvironmental factors that modulate mast cell expansion and activation. One such

modifier is hereditary alpha-tryptasemia (HαT), a germline condition caused by increased TPSAB1 copy number, which leads to elevated baseline tryptase levels and is more prevalent in patients with mastocytosis than in the general population [25, 26]. Although HαT does not initiate clonal mast cell proliferation, it is associated with enhanced mediator-related symptoms and may amplify mast cell reactivity, thereby contributing to disease heterogeneity [25]. In parallel, cytokines and their receptors (e.g., IL-4, IL-6, IL-13) contribute to the establishment of a permissive microenvironment for mast cell development and activation [16]. While polymorphisms in the genes encoding these cytokines have not been clearly linked to the development of mastocytosis, these signaling pathways may enhance mast cell responsiveness, with some evidence suggesting a more prominent role for variants in cytokine receptors, such as IL4R [25]. Collectively, these findings support a model in which cooperating somatic mutations and permissive host factors jointly shape disease phenotype and clinical variability.

3.3. Clinical manifestations

The clinical manifestations of mastocytosis are highly heterogeneous and arise from two principal mechanisms: the release of mast cell-derived mediators and the infiltration of tissues by neoplastic mast cells [1,9]. The relative contribution of these mechanisms varies depending on disease subtype, with mediator-related symptoms predominating in indolent forms and organ dysfunction becoming more prominent in advanced disease [9].

Mediator-related symptoms are among the most common clinical features and may occur episodically or persist chronically [7]. These symptoms are primarily driven by the release of histamine, tryptase, prostaglandins, leukotrienes, and cytokines [7,9]. Patients frequently report flushing, pruritus, urticaria, abdominal cramping, diarrhea, nausea, tachycardia, hypotension, syncope, and recurrent anaphylaxis [7,27]. Various triggers, including alcohol, medications, temperature changes, emotional stress, infections, and insect stings, may exacerbate symptom severity [7].

Cutaneous involvement is a hallmark feature of mastocytosis [2]. The most common presentation is maculopapular cutaneous mastocytosis (urticaria pigmentosa), characterized by hyperpigmented lesions that may urticate upon mechanical irritation (Darier’s sign). In adults, cutaneous manifestations frequently indicate underlying systemic disease [2].

Gastrointestinal symptoms are common and clinically relevant [7]. These manifestations include abdominal pain, diarrhea, nausea, vomiting, and gastroesophageal reflux, and result from both mediator release and, in some cases, mast cell infiltration of the gastrointestinal tract [7,10]. In advanced disease, complications such as hepatosplenomegaly, malabsorption, ascites, and portal hypertension may occur [7].

Skeletal involvement is also observed in systemic mastocytosis, with osteopenia, osteoporosis, bone pain, and pathological fractures reported in affected patients. In some cases, skeletal abnormalities may represent the first clinical manifestation of the disease [27].

Anaphylaxis is one of the most serious complications of mastocytosis and occurs more frequently in systemic disease. It may be triggered by hymenoptera venom, drugs, or occur without an identifiable cause, highlighting the importance of careful clinical assessment and preventive strategies [9].

3.4. Diagnosis

The diagnosis of mastocytosis requires a multidisciplinary approach because it is based on the integration of clinical, morphological, and immunophenotypic criteria, often combined with molecular studies. Due to the heterogeneous nature of the disease, accurate diagnosis is essential for appropriate classification, prognostic assessment, and therapeutic decision-making. Current diagnostic criteria are based on guidelines established by the World Health Organization and International Consensus Classification (ICC) [11, 12]. The basic requirement of one major and one minor criterion or three minor criteria for the diagnosis of SM are retained by the WHO 5th edition guidelines. In contrast, the 2022 ICC mandates only 1 major criterion or 3 minor criteria. The diagnostic workup that must be performed to fulfill the diagnostic criteria are described in subsections.

4.3.1 Serum Tryptase Measurement

Serum tryptase level is an important laboratory marker reflecting mast cell burden. A baseline tryptase level exceeding 20 ng/mL constitutes one of the minor diagnostic criteria for systemic mastocytosis. However, elevated tryptase levels are not specific and may also occur in other conditions, such as allergic reactions or myeloid neoplasms [28]. Therefore, this parameter should always be interpreted in the appropriate clinical context.

3.4.2 Skin biopsy

In cutaneous mastocytosis, typically reveals dermal infiltration by mast cells without systemic involvement. A skin biopsy should be considered in the initial diagnostic work-up if MIS is suspected and clinical manifestations are not conclusive [29].

3.4.3 Bone marrow biopsy

Histopathological analysis, particularly of bone marrow biopsy specimens, is a cornerstone in the diagnosis of systemic mastocytosis. The major diagnostic criterion defined by the World Health Organization is the presence of multifocal, dense infiltrates of mast cells (≥15 mast cells per aggregate) in the bone marrow or other extracutaneous organs. Morphologically, neoplastic mast cells often exhibit atypical features, such as spindle-shaped forms and hypogranulation.

3.4.4 Peripheral blood smear

Signs of dysplasia, monocytosis or eosinophilia should be noted. If MCL is suspected, the percentage of circulating mast cells in the peripheral blood must be determined.

3.4.5 Immunophenotyping of mast cells

Immunophenotypic analysis is essential for confirming the clonal nature of mast cells. Aberrant expression of specific surface markers distinguishes neoplastic mast cells from their normal counterparts. Key markers include: CD117 (KIT) – expressed in both normal and neoplastic mast cells, CD25 – a hallmark of clonal mast cell populations, CD2 – variably expressed, CD30 – increasingly recognized as an additional diagnostic marker in recent classifications [16, 30, 31].

3.4.6 Molecular studies

Molecular testing plays a critical role in the diagnosis of mastocytosis. The most important molecular abnormality is the activating mutation in the KIT gene, particularly KIT D816V.

The presence of a KIT mutation is considered a minor diagnostic criterion according to the World Health Organization. Additionally, identification of other mutations (e.g., in SRSF2,

ASXL1, or RUNX1 genes) may provide prognostic information, especially in advanced disease [24].

3.5 Therapeutic approaches

The management of mastocytosis is guided by disease subtype, symptom burden, and the presence or absence of organ damage. In clinical practice, the therapeutic approach differs substantially between indolent systemic mastocytosis, in which treatment is mainly directed at symptom control and improvement of quality of life, and advanced systemic mastocytosis, where the primary goals are reduction of mast cell burden, reversal of organ damage, and prolongation of survival [9, 10].

In indolent systemic mastocytosis, anti-mediator therapy remains the foundation of management. H1-antihistamines are considered first-line treatment for pruritus, flushing, and urticaria, whereas H2-antihistamines and proton pump inhibitors are commonly used in patients with gastrointestinal symptoms related to acid hypersecretion [32]. Additional agents, including leukotriene receptor antagonists and mast cell stabilizers such as sodium cromoglycate, may be considered in selected patients, particularly in the presence of persistent gastrointestinal complaints [7, 32]. Because mediator-related manifestations often fluctuate over time, treatment should be individualized according to the dominant symptom pattern and response to therapy [9].

Given the increased risk of anaphylaxis, especially in systemic mastocytosis, preventive management is essential. Patients with a history of severe hypersensitivity reactions or relevant risk factors should be prescribed self-injectable epinephrine and educated regarding trigger avoidance [9]. This is particularly important in individuals with hymenoptera venom-related reactions, recurrent unexplained anaphylaxis, or severe mediator-related symptoms [9, 27].

In advanced systemic mastocytosis, disease-modifying treatment is required. The introduction of KIT-directed therapies has substantially changed the therapeutic landscape in recent years. Midostaurin, a multikinase inhibitor, has demonstrated clinical benefit in advanced disease, including improvement in symptom burden and reduction of mast cell-related disease parameters. Avapritinib, a selective inhibitor with strong activity against KIT D816V, has further expanded treatment options and has shown marked efficacy in advanced systemic mastocytosis, with meaningful hematologic and clinical responses [10, 33].

Despite these advances, management of advanced systemic mastocytosis remains complex. Some patients may require additional cytoreductive strategies, particularly in aggressive disease, in cases with suboptimal response to KIT inhibitors, or when associated hematologic neoplasms are present [33]. In highly selected patients with refractory or very high-risk disease, allogeneic hematopoietic stem cell transplantation may be considered, although this approach is reserved for rare cases because of its significant toxicity and the need for careful candidate selection [33, 34].

Overall, current therapeutic strategies in mastocytosis combine symptomatic control, prevention of severe mediator-related events, and targeted treatment of the underlying clonal disorder. The growing availability of KIT inhibitors has significantly improved management, particularly in advanced systemic mastocytosis, although individualized and risk-adapted treatment remains essential.

3.6 Prognosis

The prognosis of mastocytosis is highly variable and depends primarily on disease subtype, molecular profile, and the extent of organ involvement. Patients with indolent forms generally have a near-normal life expectancy, with median survival exceeding 15 years, reflecting the relatively stable nature of the disease [31, 33]. In contrast, AdvSM, including ASM, SM-AHN, and mast cell leukemia, is associated with a significantly worse prognosis, with median overall survival ranging from approximately 3.5 years in ASM to less than 2 years in SM-AHN and even shorter in mast cell leukemia [33, 35]. Prognosis is strongly influenced by molecular features, particularly the burden and distribution of the KIT D816V mutation and the presence of additional high-risk mutations such as SRSF2, ASXL1, and RUNX1. A higher variant allele frequency of KIT D816V and multilineage involvement correlate with more aggressive disease and inferior survival, while the presence of multiple additional mutations is associated with an increased risk of progression and leukemic transformation [36].

In addition to molecular features, several clinical and laboratory parameters have been identified as important prognostic factors. These include the presence of organ damage (“C-findings”), cytopenias, elevated serum tryptase, alkaline phosphatase, and markers of systemic inflammation, all of which reflect disease burden and are associated with inferior outcomes [37].

These observations have led to the development of integrated prognostic scoring systems, including IPSM, MARS, and GPSM, which combine clinical, laboratory, and genetic variables to stratify patients into risk categories with distinct outcomes [33]. The International Prognostic Scoring System for Mastocytosis (IPSM) is based on readily available clinical and laboratory parameters and is applicable across both indolent and advanced disease [37]. The Global Prognostic Score for Systemic Mastocytosis (GPSM) incorporates disease subtype and organ damage, with a progression-free survival–adapted version (GPSM-PFS) designed for non-advanced disease. In contrast, the Mutation-Adjusted Risk Score (MARS) integrates high-risk somatic mutations, particularly in SRSF2, ASXL1, and RUNX1, to refine prognostication in advanced systemic mastocytosis [36]. Together, these models reflect the shift toward combined clinical and molecular risk assessment, enabling more precise prediction of outcomes and guiding individualized management strategies. Expert consensus from the European Competence Network on Mastocytosis and the American Initiative in Mast Cell Diseases supports the use of IPSM and GPSM-PFS for risk stratification in non-advanced systemic mastocytosis, while IPSM, GPSM, and MARS are recommended for patients with advanced disease [33].

4. Discussion

The findings presented in this review highlight the multifactorial nature of the disease, involving both clonal mast cell proliferation and dysregulated mediator release, which together contribute to the broad spectrum of clinical manifestations. Advances in molecular biology have substantially improved the understanding of mastocytosis pathogenesis, particularly the central role of activating KIT mutations, most notably KIT D816V. However, it is increasingly evident that this mutation alone is insufficient to explain disease heterogeneity. The presence of additional somatic mutations, especially in genes such as SRSF2, ASXL1, and RUNX1, has been strongly associated with disease progression and poorer outcomes. These findings support a multistep model of disease evolution and underscore the importance of comprehensive molecular profiling in clinical practice. From a clinical perspective, mastocytosis remains a diagnostic challenge due to its nonspecific and often fluctuating symptomatology. Therapeutically, the management of mastocytosis has evolved significantly in recent years. While symptomatic treatment remains the cornerstone of care in indolent disease, the introduction of targeted therapies, particularly KIT inhibitors. Nevertheless, challenges remain, particularly in patients with treatment resistance, advanced disease, or associated hematologic neoplasms. Despite these advances, several unmet needs

persist. Future research should focus on the development of novel targeted therapies and refinement of prognostic models integrating molecular and clinical parameters.

5. Conclusions

Mastocytosis is a rare and clinically heterogeneous disorder characterized by abnormal mast cell proliferation and activation. Its pathophysiology is driven primarily by activating mutations in the KIT gene, although additional genetic and environmental factors contribute to disease variability and progression.

The clinical presentation ranges from mild, mediator-related symptoms in indolent forms to severe organ dysfunction in advanced systemic mastocytosis. Accurate diagnosis requires a comprehensive and multidisciplinary approach incorporating clinical, histopathological, immunophenotypic, and molecular data.

Recent advances in targeted therapies, particularly KIT inhibitors, have significantly improved outcomes in patients with advanced disease. However, management remains complex and requires individualized, risk-adapted strategies.

Further research is needed to better understand disease mechanisms, identify novel therapeutic targets, and improve prognostic stratification. Continued progress in these areas is essential to optimize patient outcomes and quality of life.

Disclossure

Supplementary Materials

Not applicable.

Author Contributions

Conceptualization: AK, LS and KP
Methodology: LS, KP and AK
Software: KP;
Check: NZ, AD and JD;
formal analysis: NS;
investigation: NW;
resources: DT;
data curation: AD;

writing - rough preparation: NZ;
writing - review and editing: AK;
visualization: NS;
supervision: JR;
project administration: JR;

All authors have read and agreed with the published version of the manuscript.

Funding

No external funding was received.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgements

Not applicable.

Conflicts of Interest

Authors declare no conflicts of interest.

References:

1. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420-1427. https://doi.org/10.1182/blood-2016-09-731893
2. Valent P, Akin C, Hartmann K, et al. Updated Diagnostic Criteria and Classification of Mast Cell Disorders: A Consensus Proposal. HemaSphere. 2021;5(11):e646. https://doi.org/10.1097/hs9.0000000000000646

3. Giona F. PEDIATRIC MASTOCYTOSIS: AN UPDATE. Mediterranean Journal of Hematology and Infectious Diseases. 2021;13(1):e2021069. https://doi.org/10.4084/mjhid.2021.069
4. Wang SA, Orazi A, Gotlib J, et al. The international consensus classification of eosinophilic disorders and systemic mastocytosis. American Journal of Hematology. 2023;98(8):1286-1306. https://doi.org/10.1002/ajh.26966
5. Arock M, Hoermann G, Sotlar K, et al. Clinical impact and proposed application of molecular markers, genetic variants, and cytogenetic analysis in mast cell neoplasms: Status 2022. Journal of Allergy and Clinical Immunology. 2022;149(6):1855-1865. https://doi.org/10.1016/j.jaci.2022.04.004
6. Jackson CW, Pratt CM, Rupprecht CP, Pattanaik D, Krishnaswamy G. Mastocytosis and Mast Cell Activation Disorders: Clearing the Air. International Journal of Molecular Sciences. 2021; 22(20):11270. https://doi.org/10.3390/ijms222011270
7. Zanelli M, Pizzi M, Sanguedolce F, Zizzo M, Palicelli A, Soriano A, Bisagni A, Martino G, Caprera C, Moretti M, et al. Gastrointestinal Manifestations in Systemic Mastocytosis: The Need of a Multidisciplinary Approach. Cancers. 2021; 13(13):3316. https://doi.org/10.3390/cancers13133316
8. Leru PM. Evaluation and Classification of Mast Cell Disorders: A Difficult to Manage Pathology in Clinical Practice. Cureus. Published online February 13, 2022. https://doi.org/10.7759/cureus.22177
9. Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. Am J Hematol. 2023;98(7):1097-1116. https://doi.org/10.1002/ajh.26962
10. Sciumè M, De Magistris C, Galli N, Ferretti E, Milesi G, De Roberto P, Fabris S, Grifoni FI. Target Therapies for Systemic Mastocytosis: An Update. *Pharmaceuticals*. 2022; 15(6):738. https://doi.org/10.3390/ph15060738
11. Leguit RJ, Wang SA, George TI, Alexandar Tzankov, Orazi A. The international consensus classification of mastocytosis and related entities. Virchows Archiv. 2022;482(1):99-112. https://doi.org/10.1007/s00428-022-03423-3
12. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36(7):1703-1719. https://doi.org/10.1038/s41375-022-01613-1

13. Zanelli M, Quintini M, Magnasco S, Aprile L, Palicelli A, Zizzo M, Sanguedolce F, Ricci S, Pancetti S, Zuccalà V, et al. Mast Cell Leukemia: An Update with a Practical Review. Cancers. 2023; 15(6):1664. https://doi.org/10.3390/cancers15061664
14. Krystel-Whittemore M, Dileepan KN, Wood JG. Mast Cell: a Multi-Functional Master Cell. Frontiers in Immunology. 2016;6(1). https://doi.org/10.3389/fimmu.2015.00620
15. Ribatti D, d'Amati A. Hematopoiesis and Mast Cell Development. International Journal of Molecular Sciences. 2023; 24(13):10679. https://doi.org/10.3390/ijms241310679
16. Valent P, Akin C, Sperr WR, et al. New Insights into the Pathogenesis of Mastocytosis: Emerging Concepts in Diagnosis and Therapy. Annual Review of Pathology-mechanisms of Disease. 2023;18(1):361-386. https://doi.org/10.1146/annurev-pathmechdis-031521-042618
17. Tsai M, Valent P, Galli SJ. KIT as a master regulator of the mast cell lineage. Journal of Allergy and Clinical Immunology. 2022;149(6):1845-1854. https://doi.org/10.1016/j.jaci.2022.04.012
18. Cruse G, Metcalfe DD, Olivera A. Functional Deregulation of KIT. Immunology and Allergy Clinics of North America. 2014;34(2):219-237. https://doi.org/10.1016/j.iac.2014.01.002
19. El Hussein S, Chifotides HT, Khoury JD, Verstovsek S, Thakral B. Systemic Mastocytosis and Other Entities Involving Mast Cells: A Practical Review and Update. Cancers. 2022;14(14):3474. https://doi.org/10.3390/cancers14143474
20. Li Z. New Insights into the Pathogenesis of Systemic Mastocytosis. International Journal of Molecular Sciences. 2021; 22(9):4900. https://doi.org/10.3390/ijms22094900
21. Schwaab J, Schnittger S, Sotlar K, et al. Comprehensive mutational profiling in advanced systemic mastocytosis. 2013;122(14):2460-2466. https://doi.org/10.1182/blood-2013-04-496448
22. Nedoszytko B, Arock M, Lyons JJ, Bachelot G, Schwartz LB, Reiter A, Jawhar M, Schwaab J, Lange M, Greiner G, et al. Clinical Impact of Inherited and Acquired Genetic Variants in Mastocytosis. Int. J. Mol. Sci. 2021; 22(1):411. https://doi.org/10.3390/ijms22010411
23. González-López O, Muñoz-González JI, Orfao A, Álvarez-Twose I, García-Montero AC. Comprehensive Analysis of Acquired Genetic Variants and Their Prognostic

Impact in Systemic Mastocytosis. Cancers. 2022; 14(10):2487. https://doi.org/10.3390/cancers14102487

24. Jawhar M, Schwaab J, Schnittger S et al. Additional mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients with KIT D816V+ advanced systemic mastocytosis. Leukemia. 2015; 30(1):136-143 https://doi.org/10.1038/leu.2015.284
25. Rama TA, Gulen T. Hereditary Alpha-Tryptasemia and Mastocytosis: What We Know and What We Need To Learn. Curr Allergy Asthma Rep. 2026;26(1):19. https://doi.org/10.1007/s11882-026-01262-9
26. Polivka L, Madrange M, Bulai-Livideanu C, et al. Pathophysiologic implications of elevated prevalence of hereditary alpha-tryptasemia in all mastocytosis subtypes. J Allergy Clin Immunol. 2024;153(1):349-353.e4. https://doi.org/10.1016/j.jaci.2023.08.015
27. Li JY, Ryder CB, Zhang H, Cockey SG, Hyjek E, Moscinski LC, Sagatys E, Song J. Review and Updates on Systemic Mastocytosis and Related Entities. Cancers. 2023; 15(23):5626. https://doi.org/10.3390/cancers15235626
28. Valent P, Sperr WR, Sotlar K, et al. The serum tryptase test: an emerging robust biomarker in clinical hematology. Expert Review of Hematology. 2014;7(5):683-690. https://doi.org/10.1586/17474086.2014.955008
29. Madigan LM, Boggs NA, Rets AV, et al. Mastocytosis in the Skin: Approach to Diagnosis, Evaluation, and Management in Adult and Pediatric Patients. Am J Clin Dermatol. 2025;26(4):499-510. https://doi.org/10.1007/s40257-025-00947-7
30. Chromik K, Helbig G. Systemic mastocytosis in adults — current classification, pathogenesis, comprehensive diagnostics, and therapeutic strategies. Acta Haematologica Polonica. Published online February 11, 2026. https://doi.org/10.5603/ahp.109435
31. Ustun C, Keklik Karadag F, Linden MA, Valent P, Akin C. Systemic mastocytosis: current status and challenges in 2024. Blood Adv. 2025;9(9):2048-2062. https://doi.org/10.1182/bloodadvances.2024012612
32. Valent P, Hartmann K, Schwaab J, et al. Personalized Management Strategies in Mast Cell Disorders: ECNM-AIM User's Guide for Daily Clinical Practice. The Journal of Allergy and Clinical Immunology: In Practice. 2022;10(8):1999-2012.e6. https://doi.org/10.1016/j.jaip.2022.03.007

33. Tremblay D, Wagner N, Mascarenhas J. Management of Advanced Systemic Mastocytosis: Clinical Challenges. Journal of Blood Medicine. 2024;Volume 15:421-433. https://doi.org/10.2147/jbm.s366367
34. Ustun C, Zhang M, Peterson A, et al. Allogeneic haematopoietic cell transplantation in advanced systemic mastocytosis in the new era: A CIBMTR study. British Journal of Haematology. 2025;207(6):2486-2495. https://doi.org/10.1111/bjh.70154
35. Ike I, Samperio V, Dasanu CA. Selecting optimal therapy in systemic mastocytosis: current state and future directions. Expert Opinion on Pharmacotherapy. 2025;26(8):915-917. https://doi.org/10.1080/14656566.2025.2503847
36. Jawhar M, Schwaab J, Álvarez-Twose I, et al. MARS: Mutation-Adjusted Risk Score for Advanced Systemic Mastocytosis. Journal of Clinical Oncology. 2019;37(31):2846-2856. https://doi.org/10.1200/jco.19.00640
37. Sperr WR, Kundi M, Álvarez-Twose I, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. The Lancet Haematology. 2019;6(12):e638-e649. https://doi.org/10.1016/s2352-3026(19)30166-8