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DISEASES ASSOCIATED WITH MAST CELLS: CURRENT STATE OF THE PROBLEM

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A — концепція та дизайн дослідження; B — збір даних; C — аналіз та інтерпретація даних; D — написання статті; E — редагування статті; F — остаточне затвердження статті

Abstract. Mast cells (MCs), originating from hematopoietic stem cells, play a pivotal role in the development of numerous allergic and non-allergic diseases. Upon interaction with allergens, they become activated, leading to degranulation and the release of various inflammatory mediators that initiate an acute inflammatory response. Beyond allergopathology, MCs are implicated in the pathogenesis of a broad spectrum of conditions, including malignancies, arthritis, ischemic heart disease, osteoporosis, and other chronic inflammatory or systemic conditions. In recent years, our understanding of the role of MCs and disorders linked to their dysfunction has deepened significantly. It has been established that some of these conditions have a genetic basis, notably the KIT D816V mutation, which enhances MC functional activity and is associated with clonal diseases such as cutaneous and systemic mastocytosis (including indolent, smoldering, and aggressive forms) as well as syndromes of clonal or monoclonal MC activation. Additionally, MC activation can be secondary, occurring in response to allergic, inflammatory, or paraneoplastic processes. In certain cases, the mechanisms of this activation remain unclear, classifying these conditions as idiopathic. Furthermore, there exists a hereditary genetic syndrome — hereditary alpha-tryptasemia (HαT) – which increases the severity of allergic and anaphylactic reactions and may coexist with both clonal and non-clonal MC disorders, forming complex hybrid clinical manifestations.
The aim of this publication was to analyze existing data from scientific literature on MCs associated diseases. We aimed to detail the contemporary classification of these disorders, highlight relevant genetic defects, and outline diagnostic and targeted therapy approaches that may improve the management of affected patients.

Key words: mast cells, mastocytosis, mast cell activation syndrome, idiopathic anaphylaxis, hereditary alpha-tryptasemia, diagnosis, patient management.

Mast Cell Biology

Mast cells (MCs) were first described in the 19th century, and since then, our knowledge of their structure, functions, and involvement in pathological processes has significantly expanded [23, 27, 41, 42, 50]. Over the past decades, a range of diseases linked to MC biology and function has been identified, with MCs serving as primary effectors in allergic reactions. Their activation typically occurs in response to allergens (e. g., food, Hymenoptera venom, latex, antibiotics, pollen), leading to degranulation and the release of inflammatory mediators that trigger a pronounced acute inflammatory response [6, 7, 13]. Beyond this, MCs participate in angiogenesis, inflammation, tissue repair, modulation of innate and adaptive immunity, immune tolerance, and protection against pathogens [43, 44]. This functional versatility implicates MCs in the pathogenesis of numerous diseases, including Crohn's disease, malignancies, autoimmune disorders (Guillain-Barré syndrome, Sjögren's syndrome, vasculitides, inflammatory arthritis), multiple sclerosis, ischemic heart disease, arterial aneurysms, and osteoporosis [20, 25, 27, 42, 44]. Moreover, increased MC accumulation is observed in chronic infectious diseases (e. g., parasitic infestations, tuberculosis, syphilis), melanoma, chronic kidney and liver diseases, and systemic scleroderma [53].

Classification of Mast Cell-Related Disorders

Table 1 presents the contemporary classification of disorders associated with MC function or proliferation abnormalities. Some of these conditions are clonal, con-

firmed by mutations in the *KIT* gene (predominantly D816V) and/or CD25 expression on MC surfaces, detectable via flow cytometry or immunocytochemistry. Another group comprises hereditary disorders not necessarily involving clonality (e.g., hereditary alpha-tryptasemia [HαT], an autosomal dominant condition that may complicate both clonal and non-clonal MC disorders). Non-clonal disorders, lacking both clonal nature and hereditary mutations, include allergic, autoimmune, neoplastic diseases, paraneoplastic syndromes, and idiopathic MC activation.

Mastocytosis is a heterogeneous group of diseases characterized by the proliferation and activation of atypical MCs affecting various organs and tissues [60]. It is traditionally divided into cutaneous mastocytosis (CM) and systemic mastocytosis (SM) [61]. The key distinction between SM and CM lies in MC infiltration of at least one extracutaneous site, most commonly the bone marrow [35, 60, 61]. Clinical manifestations of mastocytosis vary widely, from isolated skin involvement in CM to severe systemic forms with organ dysfunction [61]. Diagnostic criteria for SM include:

(1) major criterion: presence of multifocal dense MC infiltrates (>15 cells/aggregate) in bone marrow or other extra-cutaneous tissue samples;
(2) minor criteria: a) ≥25 % infiltrating MCs are atypical or spindle-shaped; b) detection of a *KIT* mutation in bone marrow, peripheral blood, or extracutaneous tissue (other possible mutations include TET2, SRSF2, ASXL1, RUNX1, CBL, JAK2); c) expression of clonal MC markers such as CD25 and/or CD2, identified via immunocytochemistry or flow cytometry; d) serum tryptase level >20 ng/mL (in the absence of other myeloid neoplasms). A diagnosis of SM requires the major criterion plus one minor criterion, or ≥3 minor criteria.

CM most commonly develops in children and typically has a favorable prognosis [34]. Most cases occur before age 2, often with spontaneous regression, distinguishing pediatric forms from adult cases, where bone marrow systemic diseases are more frequent [48, 57]. Clinical forms of CM include:

– Maculopapular cutaneous mastocytosis (MPCM), the most common variant, presenting with hyper-

Table 1. Classification of Diseases Associated with Mast Cells [36]

Group of Diseases	Forms
Mastocytosis	
Cutaneous Mastocytosis (CM)*	Diffuse cutaneous mastocytosis; maculopapular mastocytosis (pigmented urticaria); cutaneous mastocytoma
Systemic Mastocytosis (SM)*	Indolent SM (including bone marrow mastocytosis); smoldering SM; aggressive SM; SM with associated hematologic neoplasm (SM-AHN); mast cell leukemia (including aleukemic form)
Non-clonal Disorders	Mast cell sarcoma
Mast Cell Activation Syndromes (MCAS)	
Primary Clonal/Monoclonal MCAS (MMAS/CMCAS)*	
Secondary MCAS	IgE-dependent allergopathology; autoimmune diseases; chronic infections; parasitic infestations; neoplasms
Idiopathic MCAS	Without established etiology
Combined Disorder	Primary MC disorder + allergopathology
Idiopathic Anaphylaxis (IA)	
Idiopathic Anaphylaxis	Without identifiable allergens (requires exclusion of α-Gal allergy and other undetected allergens)
IA Associated with Bone Marrow Mastocytosis/Clonality*	
IA Associated with CMCAS and/or HαT*	
Hymenoptera Venom Allergy + MC Disorders	
Venom Allergy Associated with Bone Marrow Mastocytosis/Clonality*	
Venom Allergy Associated with MCAS and/or Clonality*	
Bone Marrow Mastocytosis	
Hereditary Alpha-Tryptasemia (HαT)	Isolated condition or combined with CMCAS/SM/IA
Combined Forms	Various combinations of the above conditions

*Pathology with proven clonality (D816V mutation or other mutations, or CD2/CD25 expression).

pigmented nodules, papules, or macules, typically on the trunk;
– Cutaneous mastocytoma, with 1–2 nodules or plaques;
– Diffuse cutaneous mastocytosis (DCM), the rarest and most severe form, featuring diffuse thickened erythematous rashes, vesicles, and edema [3].

In children, CM diagnosis is usually based on typical skin manifestations. In adults, skin involvement often indicates SM (predominantly indolent), necessitating bone marrow biopsy [34, 57, 58, 61]. The Darier sign (blister formation in response to mechanical skin irritation) is present in most CM cases but its absence does not exclude the diagnosis [39].

SM and advanced forms of SM are characterized by multifocal dense MC infiltrates (≥15 cells per aggregate) in bone marrow or extracutaneous tissue. Minor criteria include:
– ≥25 % MCs with atypical (spindle-shaped) morphology;
– *KIT D816V* mutation;
– CD2/CD25 expression on MCs;
– Serum tryptase >20 ng/mL.

A diagnosis of SM requires one major plus ≥1 minor criterion, or ≥3 minor criteria [60]. SM classification is based on B criteria (degree of MC burden) and C criteria (organ dysfunction). Clinical forms include:
– Indolent SM (ISM), the most common form with a benign course;
– Smoldering SM (SSM);
– SM with associated hematologic neoplasm (SM-AHN);
– Aggressive SM (ASM);
– Mast cell leukemia (MCL).

ISM and SSM feature MC infiltration without clinically significant organ dysfunction. The presence of ≥1 C finding indicates ASM or MCL (≥20 % MCs in bone marrow smears). In SM-AHN, a concurrent clonal hematologic neoplasm (myeloid or lymphoid) is diagnosed [14, 61].

Bone marrow mastocytosis is typically considered a variant of ISM, while ASM, SM-AHN, and MCL are classified as advanced SM. Additional diagnostic criteria exist for specific mastocytosis variants and mast cell leukemia.
– Smoldering Systemic Mastocytosis (SSM) is diagnosed when:
– All SM criteria are met;
– ≥2 B findings are present: 30 % MCs in bone marrow/extracutaneous tissues and tryptase >200 ng/mL; dysplasia/myeloproliferation of non-MC lineage (not meeting hematologic neoplasm criteria); organomegaly (hepatomegaly, splenomegaly, lymphadenopathy) without functional impairment.
– Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN):
– The patient fulfills the diagnostic criteria for systemic mastocytosis;
– Simultaneously meets criteria for a separate hematologic neoplasm.
– Aggressive Systemic Mastocytosis (ASM):
– Fulfills diagnostic criteria for systemic mastocytosis;
– Features ≥1 organ dysfunction sign: bone marrow dysfunction with cytopenia; hepatomegaly with liver dysfunction, portal hypertension, or ascites; osteolytic lesions with pathological fractures (excluding osteoporosis); palpable splenomegaly with hypersplenism and cytopenia; gastrointestinal MC infiltration with malabsorption.
– Mast Cell Leukemia (MCL):
– Fulfills diagnostic criteria for systemic mastocytosis;
– Exhibits massive bone marrow infiltration with atypical/immature MCs; 30 % MCs in bone marrow smears; 10 % circulating MCs in peripheral blood (except in aleukemic variants).
– Mast Cell Sarcoma (MCS):
– Does not meet SM criteria;
– High-grade tumor with atypical MCs;
– High metastatic potential;
– MC activation symptoms rare (<20%);
– *KIT D816V* mutation detected in ~20% of cases.

MCS is a rare tumor characterized by localized invasive growth predominantly composed of MCs. Bone marrow changes and SM biomarkers are typically absent [45, 49, 52]. Cytologically, the tumor features atypical MC morphology. A recent study [49] found the *KIT D816V* mutation in ~20 % of cases, yet the disease remains resistant to standard therapies, with a poor prognosis and most patients surviving less than 2 years post-diagnosis.

Since mastocytosis may involve multiple organs, its clinical picture is highly variable. Common symptoms include itching, flushing, abdominal pain, nausea, vomiting, diarrhea, and bone pain [37, 55]. Skin manifestations occur in both CM and SM, ranging from localized to generalized involvement. Other symptoms include weakness, fatigue, arthralgia, myalgia, night sweats, and, in progressive cases, organ dysfunction (e.g., osteolysis, lymphadenopathy, splenomegaly, hepatomegaly, cyto-

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penia, malabsorption). Neuropsychiatric symptoms such as depression, anxiety, irritability, and mood swings may also develop [26].

Bone Marrow Mastocytosis (BMM) is a variant of ISM characterized by clonal MC proliferation exclusively in the bone marrow, without infiltration of other organs or tissues. A notable feature is its frequent association with anaphylaxis, occurring in over 90 % of BMM cases compared to 20–49 % in ISM or 0–2 % in the general population [66]. Patients with BMM typically lack skin manifestations. Bone marrow biopsy may show minimal or no MC aggregates, which complicates diagnosis and necessitates thorough immunohistochemical labeling as morphological assessement alone may be inconclusive [54].

Possible bone marrow findings in MC disorders include:

1. Classic MC aggregates, typical of SM;
2. Scattered atypical MCs without aggregates, with unusual morphology or CD25/CD2 expression, characteristic of BMM;
3. Subclinical changes meeting MCAS criteria;
4. Normal variants.

BMM typically follows an inactive course, though some patients may experience anaphylaxis to hymenoptera stings or experience idiopathic osteoporosis [67].

Anaphylaxis is a severe complication of SM, with a frequency of up to 49 %, most commonly in ISM [11]. Triggers include physical exertion, certain foods, medications, and hymenoptera stings; however, idiopathic anaphylaxis occurs without a clear trigger. Often, unexplained anaphylaxis serves as the initial clinical clue prompting detailed MC pathology investigation [51].

Idiopathic Anaphylaxis and Idiopathic Mast Cell Activation

Idiopathic anaphylaxis (IA) is characterized by recurrent anaphylactic episodes without an identifiable external trigger [29, 33]. Both MCs and basophils may contribute, with 30-60 % of adult cases and up to 10 % of pediatric cases classified as idiopathic. IA predominantly affects females and patients with atopic conditions. Described over 40 years ago, IA has a clinical classification and established treatment approaches. It typically involves ≥2 organ systems (cardiovascular, respiratory, gastrointestinal), with symptoms including urticaria, angioedema of the lips or tongue, wheezing, vomiting, diarrhea, altered consciousness, or syncope. Before diagnosing IA, sensitization to α-Gal (delayed meat allergy), primary MC disorders, and somatoform disorders must be excluded [30, 41, 47, 50]. Fatal outcomes are rare but documented.

Distinguishing IA from idiopathic MC activation can be challenging. The latter often affects young males with hypotension or syncope without skin symptoms (urticaria or angioedema), whereas IA typically involves skin manifestations [21]. Differential diagnosis includes vocal cord dysfunction, syndromes with flushing (carcinoid syndrome, pheochromocytoma, VIP-secreting tumors), vasovagal syncope, panic attacks, poisonings, and cardiopulmonary diseases.

Hymenoptera Venom Reactions and MC Disorders

Allergy to hymenoptera venom (wasps, bees) can provoke severe, potentially fatal systemic reactions [9]. Patients with SM and MCAS face a significantly elevated risk of severe reactions to stings, making timely MC pathology detection clinically critical. Additional risk factors include concurrent use of β-blockers or ACE inhibitors. Anaphylaxis to venom (especially hypotension/syncope) often indicates a clonal MC disorder [8, 9]. Routine screening for MC pathology is recommended [8, 63]. According to Bonadonna et al. [9], venom allergy is the most common allergic reaction in patients with primary clonal MC activation, occurring in 7.9 % of cases — far higher than in the general population [8, 63]. Interestingly, venom allergy is less frequent in aggressive SM, though the reason remains unclear.

Without treatment, up to 97.5 % of patients with MC disorders experience recurrent systemic reactions to hymenoptera venom, with ~90 % being severe [63]. However, venom allergy screening is unnecessary without sting reaction symptoms. Patients with confirmed IA should undergo IgE testing for bee and wasp venom extracts/components or skin prick tests [40]. A clinically significant lower threshold for sIgE to venom is >0.17 kU/L [5, 63]. Patients with SM and venom allergy require lifelong allergen-specific immunotherapy (ASIT) [5, 6, 56], despite safety concerns, as benefits outweigh risks of adverse reactions [5, 6].

Mast Cell Activation Syndrome (MCAS)

MCAS typically involves widespread damage, affecting nearly any organ — bones, liver, spleen, or lymph nodes [49]. It is a group of disorders marked by episodic MC degranulation and mediator release [62]! MCAS features pathological MC accumulation in tissues and/or abnormal mediator release. Based on etiology [1, 28, 63, 64], MCAS is classified as:

– Primary (clonal): Includes SM and its variants, CM, and clonal/monoclonal MC activation syndrome (CMCAS/MMAS);
– Secondary (non-clonal): Linked to allergopathology, autoimmune processes, infections, or neoplasms;
– Idiopathic: Without clear etiology.

Diagnostic criteria for MCAS, proposed in 2012 and updated in 2019 [64], require all three criteria:

1. Acute, recurrent MC degranulation symptoms affecting ≥2 organ systems (skin: flushing, urticaria, itching, angioedema; gastrointestinal: nausea, vomiting, diarrhea, abdominal pain; respiratory: dyspnea, wheezing, stridor; cardiovascular: hypotension, tachycardia; neuropsychiatric: syncope);
2. Elevated MC mediators (most commonly tryptase): significant increase per the formula (baseline × 1.2 + 2 ng/mL), with blood samples taken within 4 hours of symptom onset;
3. Positive response to MC stabilization or mediator blockade therapies (e.g., antihistamines, leukotriene receptor antagonists, MC membrane stabilizers, aspirin, or NSAIDs).

Modern MCAS classification includes:

1. Primary clonal/monoclonal MCAS: Does not meet SM criteria but meets MCAS criteria with clonality (*KIT D816V* in >80 % of cases or CD2/CD25 expression);
2. Secondary MCAS: Does not meet SM criteria, meets MCAS criteria, lacks clonality, with triggers like allergopathology, autoimmune diseases, infections, or tumors;
3. Combined disorder: Features clonal MC activation plus concurrent allergopathology.

MCAS diagnosis requires excluding hereditary/acquired angioedema, hypereosinophilic syndrome, neuroendocrine tumors (gastrinoma, VIPoma, medullary thyroid carcinoma, pheochromocytoma, carcinoid syndrome), endocrine disorders (adrenal diseases, hypothyroidism), and toxic, infectious, vascular, metabolic, inflammatory, or neoplastic conditions.

Hereditary Alpha-Tryptasemia (HαT)

HαT is the most common cause of elevated baseline serum tryptase levels. It features a baseline tryptase >8 ng/mL due to increased pro-alpha-tryptase production, not MC activation. This autosomal dominant condition affects ~5 % of the population, with baseline tryptase >11.4 ng/mL in 4-6 % of individuals, requiring exclusion of renal failure, infections, myeloproliferative disorders, or primary MC disorders. Tryptase genes are located on chromosome 16: *TPSAB1* encodes alpha- or beta-tryptase, and *TPSB2* encodes beta-tryptase [31]. HαT involves increased *TPSAB1* copy numbers, boosting alpha-tryptase expression.

HαT leads to α/β-tryptase tetramers activating EMR2 (CD312) receptors (increasing vascular permeability and edema) and PAR2 (F2RL1) mediators (inflammation). Tryptase also activates anaphylatoxins, the complement system, and affects coagulation [22, 32, 50]. HαT is associated with severe anaphylactic reactions, especially to hymenoptera venom, and exacerbates symptoms in SM and MCAS [66].

Patients with HαT may exhibit diverse symptoms: urticaria, angioedema, anaphylaxis, flushing, irritable bowel syndrome, neurological, pulmonary, cardiovascular, gastrointestinal, skin, and psychiatric issues [31]. Management includes baseline therapy with antihistamines or omalizumab, with efficacy (>90 % improvement in urticaria and anaphylaxis) proven [52]. Joint hypermobility and diarrhea are least responsive to treatment.

Management Strategy for Patients with Mast Cell Disorders

The primary approach to treating non-aggressive mastocytosis forms involves tailoring care to individual needs, avoiding triggers, controlling MC activation symptoms, and targeting mediator suppression. First-line drugs for managing itching and flushing include H_1-antihistamines, while H_2-antihistamines address gastrointestinal symptoms like abdominal pain, spasms, dyspepsia, and diarrhea [17, 18, 41, 51, 59]. Adjunctive therapies may include proton pump inhibitors, cromones, leukotriene receptor antagonists, and aspirin, usable even in severe cases, though long-term use risks MC activation and gastrointestinal toxicity [13, 51, 65]. For limited CM skin involvement, topical corticosteroids are effective; systemic corticosteroids or ultraviolet phototherapy are options for resistant cases [10]. Biologic therapy, particularly omalizumab, is considered individually in complex cases [2, 4, 12, 15, 16, 19, 30, 38, 46].

Mastocytosis patients should carry epinephrine auto-injectors to prevent anaphylaxis. Post-acute anaphylaxis, H_1-antihistamines and oral corticosteroids manage subacute symptoms [24, 41, 47, 51, 65]. Omalizumab (anti-IgE antibody) significantly improves symptom control and quality of life in recurrent anaphy-

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laxis cases [2, 4, 12, 15, 16, 19, 30, 38, 46]. For progressive/aggressive SM, tyrosine kinase inhibitors targeting *KIT D816V* are prescribed. The role of hematopoietic stem cell transplantation in SM remains unclear due to a lack of prospective studies establishing indications.

Thus, mastocytosis, MCAS, idiopathic anaphylaxis, and HαT are serious conditions underlying recurrent severe allergic reactions. Modern diagnostic approaches involve specific biomarkers (e.g., tryptase) and morphological studies of skin, bone marrow, and tissue biopsies. Treatment increasingly utilizes biologics and targeted inhibitors, significantly enhancing patient quality of life and controlling MC-associated disease manifestations.

ЗАХВОРЮВАННЯ, ПОВ'ЯЗАНІ З ТУЧНИМИ КЛІТИНАМИ: СУЧАСНИЙ СТАН ПРОБЛЕМИ

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Резюме. Тучні клітини (ТК), що походять з гемопоетичних стовбурових клітин, відіграють ключову роль у розвитку численних алергічних та неалергічних захворювань. При взаємодії з алергенами вони активуються, що призводить до дегрануляції та вивільнення різних медіаторів запалення, які ініціюють гостру запальну реакцію. Окрім алергопатології, ТК беруть участь у патогенезі широкого спектру захворювань, включаючи злоякісні новоутворення, артрит, ішемічну хворобу серця, остеопороз та інші. Протягом останніх років наше розуміння ролі ТК та розладів, пов'язаних з їх дисфункцією, значно поглибилося. Було встановлено, що деякі з цих станів мають генетичну основу, зокрема мутація KIT D816V, яка посилює функціональну активність ТК та пов'язана з клональними захворюваннями, такими як шкірний та системний мастоцитоз (включаючи індолентну, тліючу та агресивну форми), а також синдроми клональної або моноклональної активації ТК. Крім того, активація ТК може бути вторинною, виникаючи у відповідь на алергічні, запальні або паранеопластичні процеси. У деяких випадках механізми цієї активації залишаються незрозумілими, що класифікує ці стани як ідіопатичні. Крім того, існує спадковий генетичний синдром — спадкова альфа-триптаземія (HαT) — який посилює тяжкість алергічних та анафілактичних реакцій і може співіснувати як з клональними, так і з неклональними розладами ТК, утворюючи складні гібридні клінічні прояви.

Метою цієї публікації було проаналізувати існуючі літературні дані про захворювання, пов'язані з активацією ТК, щоб детально описати сучасну класифікацію цих захворювань, виділити відомі генетичні дефекти в їх розвитку та представити сучасні діагностичні та цілеспрямовані терапевтичні підходи, які можуть бути корисними для лікування цієї групи пацієнтів.

Ключові слова: тучні клітини, мастоцитоз, синдром активації тучних клітин, ідіопатична анафілаксія, спадкова альфа-триптаземія, діагностика, ведення пацієнтів.

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