

A literature review on childhood (cutaneous) mastocytosis and hypersensitivity reactions to medications, vaccinations and venoms

PRZEGLĄD LITERATURY NA TEMAT DZIECIĘCEJ MASTOCYTOZY (SKÓRNEJ) I REAKCJI NADWRAŻLIWOŚCI NA LEKI, SZCZEPIONKI I JADY

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Streszczenie

Mastocytosis is a disease characterized by abnormal accumulation and activation of mast cells in the body. When this accumulation occurs only in the skin, it is called cutaneous or childhood mastocytosis. However, when mast cells spread beyond the skin to other organs, it is called systemic mastocytosis. Cutaneous mastocytosis accounts for less than 5% of cases in adults, while in 90% of children with mastocytosis, the disease is limited to the skin. Mast cells produce and release chemicals to protect the body against germs and other harmful agents. Nevertheless, certain external factors can trigger and activate these mast cells. These triggers include mechanical irritation, temperature changes, heat, cold, massage, friction, certain medications (such as antibiotics, analgesics, anesthetics, opioids, and NSAIDs), venoms, and some vaccines. Vaccines having proteins and adjuvants, in particular, can overstimulate mast cells. This review will discuss drugs, venoms, and vaccines that cause excessive responses in children with cutaneous mastocytosis and how to approach these cases practically and realistically. As a result, patients with mastocytosis must receive clear guidance on which medications are safe for them and which ones they should avoid. This is because the risk of anaphylaxis in patients with mastocytosis is much higher than in the general population, and they need to be closely monitored by a doctor or healthcare provider.

Słowa kluczowe: *Komórki tuczne, mastocytosis, dzieciństwo, leki, lek, szczepionka, anafilaksja*

Summary

Mastocytosis is a disease characterized by the abnormal accumulation and activation of mast cells in the body. When this accumulation occurs only in the skin, it is called cutaneous or childhood mastocytosis. However, when mast cells spread beyond the skin to other organs, it is called systemic mastocytosis. Cutaneous mastocytosis accounts for less than 5% of cases in adults, while in 90% of children with mastocytosis, the disease is limited to the skin. Mast cells produce and release chemicals to protect the body against germs and other harmful agents. Nevertheless, certain external factors can trigger and activate these mast cells. These triggers include mechanical irritation, temperature changes, heat, cold, massage, friction, certain medications (such as antibiotics, analgesics, anesthetics, opioids, and NSAIDs), venoms, and some vaccines. Vaccines having proteins and adjuvants, in particular, can overstimulate mast cells. This review will discuss drugs, venoms, and vaccines that cause excessive responses in children with cutaneous mastocytosis and how to approach these cases practically and realistically. As a result, patients with mastocytosis must receive clear guidance on which medications are safe for them and which ones they should avoid. This is because the risk of anaphylaxis in patients with mastocytosis is much higher than in the general population, and they need to be closely monitored by a doctor or healthcare provider.

Key words: *mast cells, mastocytosis, childhood, medication, drug, vaccine, anaphylaxis*

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Introduction

Mast cells (mastocytes) are produced in the bone marrow and released into the bloodstream immaturely. After a brief passage through the blood, they migrate to their final tissue destinations, where they differentiate into mature mast cells. Mast cells are found in nearly all vascularized organs and tissues; however, they are more abundant in tissues in close contact with the external environment, such as the skin and mucosal surfaces. Mast cells are part of the white blood cells and play essential roles in the immune system, particularly in allergic reactions and anaphylaxis (1).

One of the roles of mast cells is to protect the body from foreign invaders such as bacteria, viruses, and parasites, and they also undergo hyperplasia in inflammatory states. Mast cells have receptors on their surface, the most well-known of which is FcεRI, responsible for allergic reactions, and these receptors are bound to IgE (2–4).

Mast cells are activated by various biological, chemical, and physical stimuli, and when these cells are activated, they release mediators such as histamine, heparin, prostaglandins, leukotrienes, tryptase, and chemokines. These mediators also induce vasodilation, bronchoconstriction, and the recruitment of inflammatory cells in response to the body's immune reaction (3,4). Furthermore, mediators released by mast cells are responsible for the signs and symptoms of allergic reactions and allergic diseases, such as angioedema, urticaria, itching, rash, increased vascular permeability, and anaphylaxis. These signs and symptoms can also occur in people with mast cell disorders. Because of this, it becomes challenging to distinguish between the signs and symptoms of an allergic reaction or disorder and those of mast cell disease (2,5). Although the biological functions of tryptase have not been fully explained, it is one of the most essential mediators secreted by mast cells. However, tryptase can be secreted by both mast cells and basophils. However, the tryptase secreted by mast cells is 500 times higher than that secreted by basophils (5). Therefore, serum tryptase levels are clinically considered the gold standard for mast cell disorders (6). In some cases, there is an acute rise in serum tryptase levels, showing that mast cells are involved in clinical events. In other cases, however, the tryptase concentration may show a chronic increase, indicating a mast cell increase throughout the body (7,8).

There is an abnormal increase in the number of mast cells in mast cell disorders. There may also be pathologically exaggerated infiltration of mast cells in some tissues, or they may have become more active. In such cases, the body overreacts when confronted with foreign stimuli (9,10). Such cases range from benign disorders that do not disrupt people's lives to malignant diseases that disrupt and disturb people's lives (9).

Method of selecting and analyzing the literature

A comprehensive literature search was conducted to identify relevant studies published within the last ten years. The databases searched included PubMed®, ScienceDirect®, and Wiley Online Library®. Eligible publications encompassed various articles, including original research articles, narrative reviews, systematic reviews, case reports, and meta-analyses. The search was restricted to English-language publications, and the following keywords were applied: mastocytosis, cutaneous mastocytosis, MCAS (Mast cell activation syndrome), anaphylaxis, Hymenoptera,

venom, allergy, management of mastocytosis, drug hypersensitivity, and vaccine hypersensitivity. Following these criteria, this review aims to provide an up-to-date synthesis of the current knowledge and recent advances regarding cutaneous mastocytosis and its clinical management.

Mast Cell Activation Syndrome (MCAS)

Since the discovery of mast cells in the 19th century, information about these cells, which have essential bodily functions, has been continuously obtained. Especially in the last few decades, with the development of cellular biology and molecular techniques, scientists have better understood mast cell disorders. This has led to new classifications and diagnostic approaches for MCAS and related disorders (9). While MCAS was initially defined in 2010 as a specific disease with an unknown underlying cause, in 2022, the definition of MCAS was expanded and reclassified from a term describing a particular disease to a broader, more comprehensive umbrella term that includes other mast cell diseases (10).

Thus, according to this classification, if mast cell disorders are associated with a genetic mutation, primary MCAS, such as cutaneous mastocytosis, systemic mastocytosis, or its variants, should be investigated. However, secondary MCAS should be investigated when associated with allergic, inflammatory, or neoplastic conditions. In some cases, unexplained MCAS is seen; in such cases, idiopathic MCAS should be investigated. There is also a combination of MCAS. Recently, a new group has been identified: Hereditary alpha tryptasemia (HαT) (Table 1) (7,9–12).

MCAS is a cluster of heterogeneous disorders affecting multiple organ systems, characterized by episodic symptoms triggered by mast cell activation in response to mast cell-derived substances (13). MCAS is associated with acute, severe, and excessive mast cell activation (12). As primary mast cell disorders, monoclonal MCAS, mast cell sarcoma, mast cell leukemia, and mastocytosis are rare diseases characterized by the accumulation of mast cells in the skin and other body tissues (7,14).

Table 1. In 2022, the WHO updated the classification of MCAS. (adopted from (9–12)).

Primary MCAS*	Monoclonal MCAS (MMAS)
	Clonal MCAS (SM and CM)**
Secondary MCAS	Allergic disorders
	Physical urticarias
	Chronic infection
	Neoplasia
Combined MCAS	Criteria for primary MCAS and Secondary MCAS are fulfilled
Idiopathic MCAS	No Allergy, No other reactive condition, no CM/SM and no clonal mast cells
HαT MCAS	HαT is detected and all diagnostic MCAS criteria are fulfilled

*MCAS = Mast Cell Activation Syndrome

**SM = Systemic Mastocytosis, CM = Cutaneous Mastocytosis, HαT= Hereditary alpha-tryptasemia

Mastocytosis

Mastocytosis is a rare type of mast cell disorder, characterized by the abnormal proliferation and accumulation of clonally derived mast cells in various tissues and organs. It is estimated to affect approximately 1 in 10,000 individuals (15,16). The pathogenesis of mastocytosis is related to gain-of-function somatic mutations in the KIT gene. These mutations induce the activation and phosphorylation of KIT receptors in a stem cell factor (SCF)-independent manner. Consequently, this facilitates the accumulation, differentiation, and sustained survival of mast cells (MC) across various tissues and organs (17). The KIT gene on chromosome 4 synthesizes transmembrane tyrosine kinase receptors, which play a critical role in the proliferation and survival of mast cells. Mutations in the KIT gene or pathological conditions, such as SCF (Stem Cell Factor) dysregulation, may predispose individuals to the development of mastocytosis (Figure 1)(18,19).

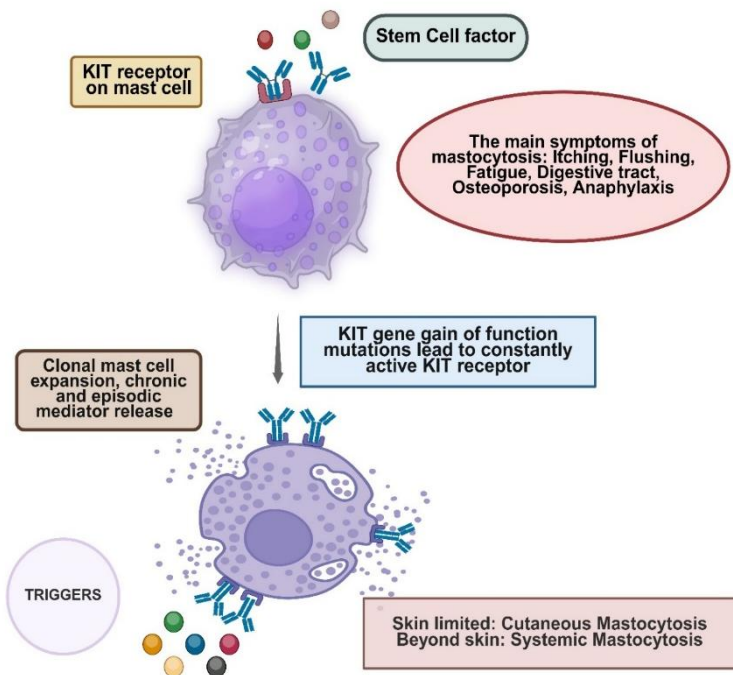


Figure 1. Pathophysiology of mastocytosis. The KIT gene is normally present in mast cells and enables the production of the c-KIT receptor. This receptor binds to stem cell factor (SCF) and transmits cell proliferation and differentiation signals. However, a mutation in the KIT gene leads to spontaneous activation of c-KIT receptors without ligand binding. This leads mast cells to grow and mature uncontrollably and to avoid apoptosis. Consequently, mast cells accumulate first in the bone marrow and other organs. (adopted from(19))(Created in <https://BioRender.com>).

According to the 2022 classification by the World Health Organization, mastocytosis is categorized into three main types: systemic mastocytosis, cutaneous mastocytosis, and mast cell sarcoma (Table 2)(17,20). Childhood-onset (cutaneous mastocytosis) and adult-onset (systemic mastocytosis) are linked to KIT

mutations; however, their progression differs. Childhood-onset mastocytosis generally follows a course that spontaneously regresses with age and remains confined to the skin. In contrast, adult-onset mastocytosis can involve other organs and tissues, with the potential to progress to hematologic neoplasms (21).

Table 2. The World Health Organization revised the mastocytosis classification in 2022. (adopted from (17,20)).

Cutaneous Mastocytosis	Urticaria pigmentosa/Maculopapular cutaneous mastocytosis
	Diffuse Cutaneous mastocytosis
	Mastocytoma of skin
Systemic mastocytosis	Indolent SM* (ISM)
	Smoldering SM (SSM)
	Bone marrow Mastocytosis (BMM)
	Aggressive systemic mastocytosis (ASM)
	Systemic mastocytosis with an associated myeloid neoplasm (SM-AHN)
	Mast Cell leukemia (MCL)
Mast Cell Sarcoma	Mast cell sarcoma (MCS)

*SM systemic mastocytosis

Generally, cases of mastocytosis in childhood are cutaneous mastocytosis, which are diagnosed by the positive presence of mast cells in skin biopsies. Cutaneous mastocytosis is divided into three main subgroups according to its clinical and histologic features. The most common form is maculopapular cutaneous mastocytosis (formerly known as urticaria pigmentosa), which accounts for about 90% of cutaneous mastocytosis cases. Maculopapular cutaneous mastocytosis manifests as yellow-brown maculopapular lesions, usually on the trunk and extremities (18,22,23). In cutaneous mastocytosis, the lesions are polymorphic, whereas in systemic mastocytosis or in adults, more monomorphic lesions are reported (24).

Another form of cutaneous mastocytosis is diffuse cutaneous mastocytosis, representing about 5% of all mast cell disorders in children. However, the morbidity and mortality rates associated with this form are higher than those of the other subtypes (25). Patients with diffuse cutaneous mastocytosis typically show a "peau d'orange" appearance of the skin, hyperpigmentation, and Darier's sign—key disease characteristics. These features are considered specific diagnostic indicators (26). The other subgroup of cutaneous mastocytosis is mastocytoma (20).

There is another form of mastocytosis, systemic mastocytosis, which is typically observed in adulthood. Systemic mastocytosis is an aggressive disorder involving the bone marrow, gastrointestinal tract, liver,

spleen, lymph nodes, and other organs throughout the body, with skin infiltration occurring in rare instances (24,27–29).

According to the World Health Organization's 2022 classification, systemic mastocytosis is classified into subgroups. These subgroups range from mild clinical manifestations to rare aggressive forms. Systemic mastocytosis is classified into indolent SM (ISM), smoldering SM (SSM), and advanced SM (AdvSM) based on clinical parameters, organ involvement, and histological criteria. Furthermore, the advanced SM category is further subdivided into SM with associated hematologic neoplasms (SM-AHN), aggressive SM (ASM), and mast cell leukemia (MCL) (12,30). In 2022, bone marrow mastocytosis (BMM), one of the non-aggressive subtypes of systemic mastocytosis recognized by the World Health Organization, typically follows a benign course (31). Among the subtypes of systemic mastocytosis, indolent SM is the most commonly encountered form and generally exhibits a favorable prognosis. However, some cases progress to the aggressive form or smoldering SM (SSM) (30). Although rarer, smoldering SM (SSM) presents a greater disease burden than indolent SM (ISM).

Additionally, it is associated with a lower survival rate based on observed cases (32). Advanced forms of systemic mastocytosis are associated with a poor prognosis, like smoldering SM (SSM), and may result in organ damage. Furthermore, these patients may develop complications, including severe anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, and leukocytosis (31,33). Although mast cell leukemia constitutes only 1% of the pathologies associated with systemic mastocytosis, it is the disease with the highest mortality rate within this condition (33). Skin biopsy and extra-dermal organ biopsy can be performed to diagnose systemic mastocytosis. Biopsy results may show an increased infiltration of mast cells.

Furthermore, if the patient has an elevated serum tryptase level (above 20 ng/mL), this may strongly support the diagnosis of systemic mastocytosis. However, elevated serum tryptase levels can also be seen in some types of cutaneous mastocytosis. In systemic mastocytosis, more mast cell infiltration can be observed when biopsies are taken from other organs besides the skin. Pathologic screening for these patients' KIT (D816V) mutation increases the likelihood of detecting an abnormality (34–36).

Hypersensitivity to Drugs in Cutaneous Mastocytosis

Mast cells in the human body are one of the most functionally critical cells in the body. These cells act as a component of the immune system, and when they encounter foreign pathogens entering the body, they release various chemicals to destroy them. However, temperature changes, cold, stress, spicy foods, massage, alcohol, pressure, and sun exposure can cause mast cells to become activated (37,38). In addition, certain medications (antibiotics, analgesic opioids, anesthetics, muscle relaxants, and NSAIDs) can cause mast cell activation. (Table 3)(38–40).

Table 3. The factors that cause activation of mast cells in patients with mastocytosis (adopted from (38–40)).

Insect stings, envenomation
Hymenoptera
Jellyfish
Snake
Changes in temperature
Cold
Heat
Mechanical irritations
Massage
Frication
Pressure
Medications
Some antibiotics (Vancomycin, fluoroquinolones)
Anesthetic substances
Opioid analgesics (Codeine, Morphine)
Radiocontrast media (iodinated)
Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)
Muscle relaxants
Sympathomimetic Drug (Phenylephrine)
Other
Alcohol (in medications, as beverages)
Emotional stress
Exercise
Spicy foods
Infections (viral, bacterial, parasitic)
Fever
Invasive procedures (Surgery, biopsies, Endoscopy)

In children with mastocytosis, there is already an excessive accumulation and activation of mast cells. When these children are exposed to agents that stimulate mast cells, the excess mast cells can cause more severe reactions. As a result, this can lead to serious and life-threatening conditions such as anaphylaxis (41).

The cause of anaphylaxis in patients with cutaneous mastocytosis is usually idiopathic; however,

a significant proportion of anaphylactic reactions in these patients are due to drugs and foods. Drugs are a widespread trigger of non-clonal MCAS. Activation of mast cells and release of granules within them can occur either IgE-independently or through cross-linking of IgE-specific receptors on the surface of mast cells (Figure 2)(7,41,42)

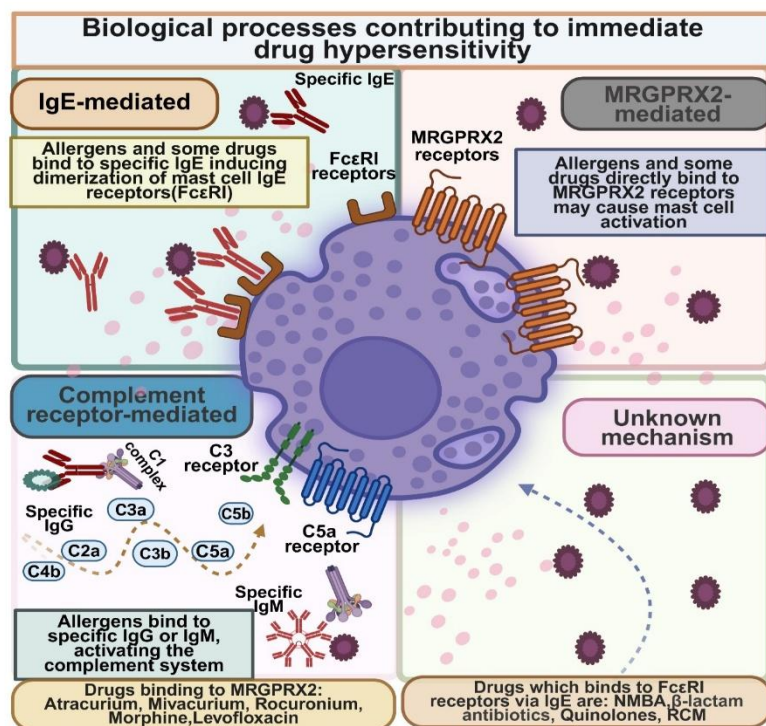


Figure 2. Drug Hypersensitivity Pathways Associated with Mastocytosis. Certain factors and drugs can trigger mast cells to release mediators in normal individuals. However, this occurs differently and more pronouncedly in patients with mastocytosis. In patients with mastocytosis, abnormal mast cell accumulation and activation are already present. When these patients are exposed to certain triggers or drugs, they release excessive amounts of mediators through different pathways than normal individuals. This can lead to clinically more severe and uncontrolled reactions. (adopted from((42))(Created in <https://BioRender.com>).

The following medications have been identified as potential triggers for severe reactions in children diagnosed with cutaneous mastocytosis:

1. Antibiotics

We have limited data on the development of tolerance between antibiotic drugs and patients with cutaneous mastocytosis. However, in the current scientific literature, it is frequently emphasized that serum basal tryptase levels should be monitored in case of severe drug reactions. Among antibiotics, beta-lactams are the most common group causing hyperreactivity. In addition, several antibiotics, including fluoroquinolones and vancomycin, have been associated with adverse reactions (41,43).

In a study of 133 children diagnosed with cutaneous mastocytosis, reactions to drugs were investigated.

According to the data obtained, responses were observed in 12 patients: (6 for beta-lactams, 3 for acetaminophen, and 2 for the measles, mumps, and rubella (MMR) vaccine) (41,44). Additionally, in another case, a girl receiving ceftriaxone developed anaphylaxis and loss of consciousness, accompanied by an increase in serum basal tryptase levels following drug administration (41). A patient with cutaneous mastocytosis is at a higher risk of developing anaphylaxis after exposure to triggers compared to healthy children. However, when compared to patients with systemic mastocytosis, the incidence of anaphylaxis is lower. Further research is required to define the frequency of allergic reactions to antibiotics in different subtypes of mastocytosis, such as systemic and cutaneous mastocytosis (38,45,46). The basophil activation test (BAT) is beneficial for risk stratification of patients before provocation tests with certain drugs and is traditionally employed to assess penicillin allergy (44). MRGPRX2 is a novel G-protein-coupled receptor found on mast cells, and its expression level is increased, especially in patients with cutaneous mastocytosis. An increase in these receptors is observed in conditions such as cutaneous mastocytosis and urticaria (44,46). Some pharmacologic substances, especially drugs carrying the chemical skeleton of tetrahydroisoquinoline (THIQ), have been shown to interact with this receptor and activate mast cells. These drugs include NSAIDs, succinylcholine, opiates, quinolone group antibiotics, neuromuscular blocking agents, and vancomycin (47). This pathway, mediated through MRGPRX2, activates mast cells by an IgE-independent mechanism. Use of such drugs is therefore not recommended in patients with mastocytosis (44).

2. Anesthetic agents

Some drugs used as sedatives and hypnotics in surgery, such as analgesics, hypnotics, neuromuscular blocking agents (NMBAs), and opioids, can cause mast cell activation through different mechanisms (48). In patients with mastocytosis, these drugs may trigger anaphylaxis by activating mast cells through either IgE-dependent or IgE-independent pathways (49). Several sources have reported that anesthetic medications, NSAIDs, antibiotics, and opioids can lead to fatal anaphylaxis (41). Because natural opioids often cause dose-dependent mast cell activation, they are not considered suitable for use in children with mastocytosis. This group includes buprenorphine, codeine, meperidine, and morphine.

In contrast, another class of opioids induces only minimal mast cell activation and does not lead to significant increases in histamine or tryptase levels. This group includes the piperidine derivatives alfentanil, fentanyl, sufentanil, and naloxone. Furthermore, synthetic opioids such as oxycodone, hydromorphone, and tramadol have demonstrated similarly low histamine responses in vitro studies. Therefore, these agents are considered safer for patients with mastocytosis (44).

In a retrospective study, 22 children with mastocytosis underwent general and local anesthesia as part of a sedation procedure. As a result, 18% of the patients experienced gastrointestinal tract (GI) related discomfort, and 9% experienced only skin rash. Patients were not given any medication for prophylaxis. Based on these findings, general anesthesia is considered a potentially risky procedure for patients with mastocytosis (41,44,50). In another study, a total of 50 anesthetic procedures were performed in 48 children with mastocytosis undergoing surgery. Among these

procedures, only one case of perioperative anaphylaxis was reported. However, the child who experienced anaphylaxis was able to tolerate the same anesthetic protocol without complications in a subsequent procedure (50). A detailed anamnesis should be obtained from all patients with mastocytosis before surgical intervention, including information on previous drug reactions and specific anesthetic agents that have caused adverse responses. Based on this evaluation, the choice of drugs should be individualized. Opioids and NMBAs are the most commonly implicated drug classes in perioperative adverse reactions. Scientific data indicate hypersensitivity reactions are more frequently associated with non-depolarizing NMBAs such as atracurium, mivacurium, and rapacurium. Therefore, the use of these agents is not recommended during the perioperative period in patients with mastocytosis. These drugs have been shown to activate mast cells through an IgE-independent mechanism, specifically via the MRGPRX2 receptors (44,51).

There is limited information in the literature regarding the occurrence of adverse reactions to local anesthetic agents in patients with mastocytosis. However, it is generally recommended that amide-type local anesthetics (e.g., lidocaine) be preferred in clinical practice (26). On the other hand, it has been reported that ester-type local anesthetics such as benzocaine, chlorprocaine, procaine, and tetracaine may activate mast cells and induce histamine release, which may result in severe adverse reactions, including anaphylaxis, particularly in pediatric patients with mastocytosis. Therefore, using ester-type local anesthetics in this patient group should be avoided (41,44,52). Agents considered safe for use in sedation procedures include ketamine, midazolam, and propofol. Reports of anaphylaxis associated with these agents are exceedingly rare, and only a few scientific publications have documented such reactions.

Additionally, sevoflurane, an inhalational anesthetic commonly used to maintain general anesthesia, has been shown to inhibit mast cell activation (41). The anesthesiologist should be informed of the patient's mastocytosis subtype, the extent of mast cell activation (e.g., bullous skin lesions or pruritic inflammatory dermatoses), and baseline serum tryptase levels before the procedure. As with adult patients, pediatric patients presenting with widespread skin involvement and active bullous dermatologic manifestations require cautious anesthetic management (41). Individuals with a history of perioperative anaphylaxis constitute a high-risk group. To optimize perioperative safety, a comprehensive history of prior surgical procedures and any adverse reactions to anesthesia should be obtained in all patients with mastocytosis (41,53).

3. Non-steroidal anti-inflammatory drugs (NSAIDs)

In patients with mastocytosis, the increased number of mast cells and their tendency to release an excessive amount of mediators upon stimulation render certain drug groups potentially hazardous. Among these, NSAIDs are known to trigger anaphylaxis and systemic reactions in both adults and children. However, the impact of NSAIDs appears to be less pronounced in pediatric patients compared to adults, and the associated risk is reported to be lower in children with mastocytosis (41,54). To evaluate the side effects and hypersensitivity reactions associated with NSAIDs, a study was conducted involving 111 pediatric patients diagnosed with mastocytosis. Various NSAID-class

drugs were administered to these patients, and potential adverse reactions were monitored. At the study's conclusion, hypersensitivity reactions were observed in only four patients. Among these, two patients developed both angioedema and urticaria, one patient developed only urticaria, and one developed angioedema alone. The drugs implicated in these reactions included diclofenac, ibuprofen, dipyron, and a multivitamin preparation (55). In a study conducted in Spain, 681 patients diagnosed with systemic and cutaneous mastocytosis were evaluated. The findings indicated that 91% of pediatric patients tolerated NSAIDs, compared to 87% of adult patients (56).

Another study conducted in the Asia-Pacific region reported that both pediatric and adult patients with mastocytosis may develop drug-induced hyperreactivity associated with the use of NSAIDs. The same study further demonstrated that the development of NSAID-induced respiratory disorders, dermatological reactions, urticaria, and angioedema occurred more frequently following NSAID use than the development of classical drug allergies (57).

Studies have demonstrated that the use of NSAIDs, such as aspirin, in patients with mastocytosis is associated with an increased risk of urticaria and angioedema (48,54). In pediatric patients with NSAID intolerance, paracetamol (acetaminophen) is recommended as an alternative (44,56). In conclusion, patients with mastocytosis are more susceptible to hypersensitivity reactions induced by NSAIDs. Therefore, it is recommended that children with mastocytosis avoid NSAIDs. Instead, alternative treatment options associated with fewer side effects or that do not trigger drug allergies should be considered (58).

Despite existing research on NSAIDs, there remains insufficient information regarding the allergic reactions and side effects of this drug group in patients with mastocytosis. Consequently, additional studies are necessary better to elucidate the effects of NSAIDs on individuals with mastocytosis.

4. Radiocontrast media

Overall, it remains controversial whether patients with mastocytosis have an increased risk of anaphylaxis to radiocontrast agents compared to the general population (48,59). Two main pathways by which radiocontrast agents activate mast cells have been identified. The first of these is the IgE-dependent pathway. This mechanism may activate mast cells through specific IgE antibodies directed against the radiocontrast agent. However, there are limited data in the literature, and the frequency of anaphylaxis or hypersensitivity reactions associated with this pathway has been reported to be low (57). The second pathway is independent of IgE. In this mechanism, radiocontrast agents can directly activate mast cells. Although anaphylactic reactions associated with this pathway are rare, it has been reported that anaphylaxis may develop with a frequency of less than 1% in the general population (40,41,60).

Non-ionic and hyperosmolar radiocontrast media are associated with a higher incidence of drug-induced hypersensitivity reactions (57). Studies show hypersensitivity reactions to gadolinium-based contrast agents (GBCA) have been elevated (61).

Although radiocontrast media (RCM) are not among the most common triggers of anaphylaxis in patients with mastocytosis, epidemiological data on this topic are limited (44,48). In patients with mastocytosis, antihistamines and corticosteroids are recommended to manage potential adverse reactions following RCM

administration and stabilize the patient's condition (40,48).

In patients who experience this type of reaction, skin prick testing (SPT) is recommended to reduce the risk of hypersensitivity reactions and adverse events during subsequent exposures (48,57). However, one disadvantage of this test is the high rate of false positives in these patients. Therefore, SPT is insufficient for detecting hypersensitivity reactions and anaphylaxis that may develop in response to radiocontrast agents and other drugs (26,62).

Hypersensitivity to Vaccinations in Cutaneous Mastocytosis

Vaccination is essential for immunizing individuals within a population and reducing the spread of infectious diseases. In addition to providing individual protection, vaccination significantly reduces the incidence of morbidity and mortality at the community level. This, in turn, contributes to the overall quality of life (48). Although rare, some individuals may experience mild side effects following vaccination, such as redness, swelling, or local reactions at the injection site. In some instances, a temporary elevation in body temperature is also seen. These adverse effects are generally mild, self-limiting, and negligible compared to the substantial protective benefits of vaccination (63,64).

IgE-dependent adverse reactions to vaccines are rare but may occur. These reactions are typically triggered by additives or residual components remaining from the manufacturing process. Identified allergens include dextran, gelatin, yeast, latex, neomycin, thimerosal, casein, and polymyxin B (48,65). Both anaphylactic and non-anaphylactic reactions following vaccination should be thoroughly evaluated. If IgE-mediated sensitization to a vaccine is suspected, measuring specific serum IgE levels is recommended to assess the potential risk for future vaccinations (48,64,66).

In individuals with mastocytosis, particularly pediatric patients, vaccines may act as potential triggers for hypersensitivity reactions (65). Although the overall risk of vaccine-related adverse reactions in children with mastocytosis is considered low, an increased incidence of hypersensitivity to exogenous agents, including medications, has been reported in this population. Nevertheless, clinical guidelines in the United States and Europe recommend administering all vaccines in national immunization schedules for patients with cutaneous mastocytosis (48,67). Following vaccination, individuals with mastocytosis may experience symptoms such as angioedema, bullous lesions, pruritus, urticaria, and gastrointestinal manifestations. These reactions are primarily attributed to mast cell activation induced by active ingredients or excipients in the vaccine, leading to an exacerbation of symptoms (68). In a retrospective study, four patients developed vaccine-related adverse reactions after the first dose of the hexavalent vaccine was administered to a group of 72 cutaneous mastocytosis patients. One of these patients was diagnosed with maculopapular cutaneous mastocytosis, one with mastocytoma, and the remaining two with diffuse cutaneous mastocytosis (69). The most common vaccine-related adverse reaction was generalized urticaria, which usually developed within 2 to 4 hours following vaccination (48).

Adverse reactions to hexavalent vaccines, which include pertussis, diphtheria, tetanus, poliovirus,

Haemophilus influenzae type B, and hepatitis B, have been seen in children with mastocytosis. Nevertheless, existing literature suggests that these reactions are typically mild and that subsequent vaccine doses are generally well tolerated (70). In contrast, there is limited data regarding adverse responses to trivalent vaccines such as measles-mumps-rubella (MMR), meningococcal, or varicella (64). From a general perspective, children diagnosed with mastocytosis may have a slightly higher likelihood of experiencing adverse vaccine reactions compared to their healthy peers. However, these reactions are typically mild and resolve spontaneously within a brief period. Moreover, it has been observed that such adverse reactions do not recur following repeat dose administrations (70,71).

The observation that adverse reactions occurred exclusively after hexavalent vaccine administration suggests that monovalent vaccines may represent a safer alternative, particularly in patients with diffuse cutaneous mastocytosis (71). In pediatric patients with mastocytosis, there is a slight increase in the rate of anaphylaxis after vaccination (70). Because of this, it is recommended that these patients carry an epinephrine autoinjector during and after vaccination. According to data in the literature, these children should be monitored under the supervision of healthcare personnel for at least 30 minutes to 1 hour after vaccination (72). In addition, it is essential to provide detailed training to the parents of the patients on how to use the epinephrine autoinjector (71).

Hymenoptera venoms

The order Hymenoptera includes many insect families such as Apidae (bees), Vespidae (wasps), and Formicidae (ants). However, some of the substances in the venoms injected into the bodies of humans by the stings of species belonging to the Apidae and Vespidae families can cause anaphylaxis and serious health problems (73,74). These reactions develop in the body based on IgE (75). Some risk factors for anaphylaxis due to Hymenoptera venom include gender, age, systemic mastocytosis, and elevated basal serum tryptase levels. The relationship between systemic mastocytosis and Hymenoptera venom has been known to scientists for many years. In patients with systemic mastocytosis, this may lead to reactions ranging from mild anaphylaxis to severe and even fatal outcomes. Hymenoptera venom-associated anaphylaxis deaths are among the leading causes of anaphylaxis-related fatalities worldwide (75). In such cases, or when there is a risk of anaphylaxis in patients with mastocytosis, whether drug-induced or due to other causes, preventive treatment with omalizumab, corticosteroids, and antihistamines should be considered (76,77).

According to the literature, venom immunotherapy (VIT) is the most effective treatment after Hymenoptera venom-induced anaphylaxis in patients with systemic mastocytosis (75). I want to point out that there is an inverse relationship between Hymenoptera venom and age, because the rate of anaphylaxis in any local or systemic reaction due to Hymenoptera venom is low in children, and this risk increases in parallel with age (74,78).

Management of Hypersensitivity Reactions to Medications, Vaccinations, and Venoms

The first step in managing cutaneous mastocytosis is to keep children with mastocytosis away from all triggering factors as much as possible. Therefore, patients and their families should be thoroughly informed about the need to be cautious about provoking factors such as stress, temperature changes, sleep deprivation, humidity, and spicy foods. In addition, it is also essential to educate families about medications that can worsen the disease (79,80). Furthermore, when children need to be vaccinated or undergo surgical intervention, the patient's mastocytosis status must be reported to the relevant physician (80). This is important because children with mastocytosis have a higher incidence of anaphylaxis than healthy children (81). Therefore, using an epinephrine auto-injector should be thoroughly taught to the patient and their family, and the auto-injector should always be kept with the patient (71). When symptoms such as urticaria pigmentosa develop in a child with cutaneous mastocytosis, H1 antihistamines may be used. However, H2 antihistamines such as simetidine and famotidine may be preferred to alleviate or eliminate gastrointestinal symptoms. Proton pump inhibitors may also be added to the treatment for a more effective result (79,80).

In children with mastocytosis, moderate or low-potency glucocorticoids may reduce the skin's recurrent itching and cosmetic issues (79). On the other hand, in cases requiring surgical intervention, it is essential to have adrenaline and isoflurane available during the perioperative period. Additionally, medications such as acetaminophen (paracetamol) should be available to address any unexpected complications arising during the postoperative period (79,80). The follow-up of children with cutaneous mastocytosis should be conducted by calculating the SCORMA Index (24,80).

Discussion of the previous literature

Mastocytosis is a disease characterized by the accumulation and proliferation of abnormal mast cells. One of its subtypes, cutaneous mastocytosis, occurs exclusively in the skin during childhood (24). This condition generally has a favorable prognosis, with spontaneous regression observed in approximately 90% of cases as age progresses (80). Nevertheless, in these patients, certain factors such as chemical agents, temperature changes, stress, trauma, medications, and vaccinations may increase the risk of adverse reactions and anaphylaxis (38).

Although the risk of anaphylaxis is higher in children with mastocytosis compared to the general population, in childhood mastocytosis, anaphylaxis is more frequently idiopathic in origin; however, the literature tends to emphasize medications as the principal cause. It should also be noted that physical or mechanical factors are at least as important as drugs in triggering mast cell degranulation. In children with mastocytosis, various drugs—including antibiotics, NSAIDs, RCM, and opioids—have been reported as potential triggers of anaphylaxis. However, no systematic evaluation has been conducted specifically in pediatric populations, and only a limited number of studies have been published. Therefore, drawing definitive conclusions remains challenging. Current evidence suggests that among medications, NSAIDs stand out as the primary pharmacological triggers of anaphylaxis (41).

This review has compiled and synthesized the literature on cutaneous mastocytosis published in the last decade. We aimed to provide researchers with easier access to up-to-date information while highlighting the existing knowledge gap in this area. For this reason, further studies are needed to elucidate better the mechanisms by which drugs contribute to mast cell activation in patients with cutaneous mastocytosis. With future evidence, it will be possible to more clearly determine which medications can be safely used in these patients and which should be strictly avoided. To achieve this, multicenter and comprehensive studies are required. Moreover, providing accurate information and education to patients and their families is essential, considering new literature.

Conclusion

Cutaneous mastocytosis generally has a better prognosis than systemic mastocytosis and often resolves spontaneously. However, some drugs and vaccine ingredients can cause increased adverse reactions and even severe conditions such as anaphylaxis in children with mastocytosis. Therefore, it is essential to take a detailed anamnesis in children with mastocytosis and to inquire about previously used drugs, vaccine responses, and family history. To manage possible complications effectively, it is recommended that a pediatrician and allergy-immunology or hematology specialists closely monitor these patients. In addition, only drugs and vaccines with proven safety and a minimal risk of side effects should be administered to these children. The limited data on this topic in the literature highlights the need for further scientific research.

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