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REVIEW

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Drug Allergy in Systemic Mastocytosis: Points to Consider

Eda ASLAN, Nihal METE GOKMEN, Aytul Zerrin SIN

Department of Internal Medicine, Division of Allergy and Immunology, Ege University Faculty of Medicine Hospital, Izmir, Türkiye

Corresponding Author: Eda Aslan ✉ edaarslan_91@hotmail.com

ABSTRACT

Mast cell diseases are a group of rare diseases with a broad clinical spectrum that develop as a result of abnormal proliferation or uncontrolled activation of mast cells. Systemic mastocytosis, one of these diseases, is characterized by the accumulation and activation of mast cells in various organs, primarily the bone marrow, but also the skin, liver, spleen, and gastrointestinal system. Clinical presentations can vary from mild symptoms such as skin redness and itching to life-threatening reactions such as cardiovascular instability and anaphylaxis. Drug-induced hypersensitivity reactions are a significant clinical problem in patients with mastocytosis. Nonsteroidal anti-inflammatory drugs, antibiotics, radiocontrast agents, and perioperative agents are the main risk groups of drugs. These reactions may arise through immunological IgE-mediated mechanisms or direct stimulation of mast cells via receptors such as MRGPRX2. The potential for drug-induced reactions in individuals with mastocytosis is a cause for concern among physicians and patients, leading to unnecessary drug restrictions and mislabeling of allergies in clinical practice. This situation may limit patients' access to appropriate treatment and negatively affect their quality of life. This review summarizes the pathophysiological mechanisms underlying the risk of drug hypersensitivity in patients with mastocytosis, the factors contributing to the development of reactions, and safe management strategies based on the current literature. The aim is to improve understanding of the risks associated with drug use in mast cell disorders, prevent unnecessary pharmacological restrictions, support appropriate treatment approaches, and thereby enhance the efficacy and safety of patient management.

Keywords: Systemic mastocytosis, mast cell disorders, drug hypersensitivity reactions, anaphylaxis

INTRODUCTION

Mast cell disorders are a heterogeneous group of diseases associated with abnormal or uncontrolled activity of mast cells, including a variety of clinical presentations. The three main forms of mast cell disorders are mastocytosis, mast cell activation syndrome (MCAS), and hereditary alpha-tryptasemia (HαT). Mast cell activation syndrome (MCAS) typically presents with recurrent anaphylaxis attacks of varying severity that affect multiple organ systems. In addition to a significant increase in serum tryptase levels or other mast cell mediators following the onset of systemic symptoms, a positive clinical response to mast cell stabilizers or mediator blockers supports the diagnosis.

MCAS can be classified into different etiological subtypes. If there is an increase in monoclonal mast cells carrying a KIT mutation, the condition is classified as monoclonal MCAS. Otherwise, if the condition has developed secondary to a benign condition such as immunoglobulin E-mediated allergic diseases, it is classified as secondary; if no cause or clonality can be identified, it is classified as idiopathic (1).

Mastocytosis is a group of diseases with clinically variable phenotypes; this spectrum includes subtypes such as cutaneous mastocytosis, systemic mastocytosis (SM), and mast cell sarcoma (2).

Systemic mastocytosis is a rare myeloproliferative disorder characterized by the infiltration and functional activation of mast cells showing clonal proliferation in various organs and tissues, primarily the skin, bone marrow, spleen, lymph nodes, liver, and gastrointestinal system (3-5).

ORCID Eda Aslan / 0000-0002-3126-3394, Nihal Mete Gokmen / 0000-0002-2450-5439, Aytul Zerrin Sin / 0000-0002-9199-1991

Table I: World Health Organization (WHO) classification of mastocytosis

Cutaneous mastocytosis (CM)	• Maculopapular cutaneous mastocytosis (MPCM) • Diffuse cutaneous mastocytosis (DCM) • Mastocytoma of skin
Systemic mastocytosis (SM)	Nonadvanced SM variants • Bone marrow mastocytosis (BMM) • Indolent SM (ISM) • Smouldering SM (SSM)
	Advanced SM variants • SM with associated hematologic neoplasm (SM-AHN) • Aggressive SM (ASM) • Mast cell leukemia (MCL)
Mast cell sarcoma	

Mastocytosis can present as a cutaneous form, systemic form, and mast cell sarcoma. Systemic mastocytosis (SM) can be classified into two groups: non-advanced forms and advanced forms. Non-advanced forms include bone marrow mastocytosis (BMM), indolent mastocytosis (ISM), and smoldering mastocytosis (SSM). Advanced forms can be grouped into aggressive SM (ASM), mast cell leukemia (MCL), and SM associated with other hematological malignancies (SM-AHN) (Table I).

Clonal mast cells, which increase in systemic mastocytosis, often carry mutations in the KIT proto-oncogene. The most common of these is the KIT D816V mutation, which has become the pharmacological target of tyrosine kinase inhibitors developed in recent years. The clinical symptoms associated with the disease result from the release of mast cell mediators. During this process, biologically active mediators such as tryptase, histamine, prostaglandins, and leukotrienes released from mast cells can cause various systemic symptoms such as flushing, abdominal pain, nausea, vomiting, diarrhea, gastrointestinal symptoms, dizziness, chronic fatigue, headache, hypotension, and anaphylaxis in severe cases (6,7). Anaphylaxis is one of the most serious and potentially life-threatening clinical manifestations of systemic mastocytosis.

The prevalence of atopy in individuals with mastocytosis is similar to that in the general population. However, it has been reported that if there are accompanying allergic diseases, the symptoms of this disease tend to be more severe. For example, severe systemic reactions, including anaphylactic shock, may develop following Hymenoptera bee stings or during venom immunotherapy. However, in some cases, recurrent and unexplained (idiopathic) anaphylaxis may be the first manifestation of mastocytosis (8). Although bee stings are the most common cause of anaphylaxis in mastocytosis patients, the second most common cause is idiopathic anaphylaxis that occurs spontaneously without a trigger (9,10). In more severe forms of the disease, organ dysfunction develops due to the infiltrative accumulation of mast cells.

MAST CELL DISEASES AND DRUG ALLERGY

Mast cell activation can be triggered by various specific and nonspecific stimuli. In clinical practice, the main agents thought to cause this activation include nonsteroidal anti-inflammatory drugs (NSAIDs), vaccines, opioid-derived analgesics, neuromuscular blocking agents, radiocontrast agents, and antibiotics. There are numerous case reports in the literature regarding reactions that develop with these agents. However, the true incidence and prevalence of mast cell-mediated hypersensitivity reactions associated with these drugs remain unclear. Furthermore, there are insufficient studies comparing the risk levels associated with sensitivity differences between cutaneous mastocytosis and the systemic form (11).

In a recent analysis of 2,485 adult mastocytosis patients in the European Competence Network on Mastocytosis (ECNM) database, risk factors associated with potential triggers related to drugs and other environmental agents were evaluated in detail. According to the findings, 38.1% of patients reported at least one hypersensitivity reaction (HR). In cases of cutaneous mastocytosis and indolent systemic mastocytosis (ISM), the most commonly reported trigger was Hymenoptera venom, while in advanced systemic mastocytosis, the primary causes of these reactions were nonsteroidal anti-inflammatory drugs (NSAIDs) and penicillin-group antibiotics (12).

In a more recent retrospective study involving 470 adults diagnosed with clonal mast cell disease, drug-induced HRs were evaluated. The results of this study showed that the overall incidence of drug-induced anaphylaxis in patients diagnosed with SM, cutaneous mastocytosis, and MCAS was 6.3%. Drug-induced anaphylaxis was found to account for one-third of confirmed drug hypersensitivity reactions in patients with mastocytosis. The most frequently implicated causative agents were non-steroidal anti-inflammatory drugs (NSAIDs), accounting for 56% of cases, followed by perioperative medications (23%) and antibiotics (13%). Hypotensive syncope was observed in 43% of cases with anaphylaxis. The most notable finding from this study is that all reported drug-related reactions occurred before the patients were diagnosed with mastocytosis (13).

MECHANISMS OF MAST CELL ACTIVATION IN DRUG REACTIONS

Important stimulatory receptors found on the surface of mast cells include high-affinity immunoglobulin E (IgE) receptors, immunoglobulin G (IgG) receptors, Toll-like receptors (TLRs), stem cell factor (SCF) receptors, receptors for complement proteins, cytokine receptors (e.g., for interleukin [IL]-33 and thymic stromal lymphopoietin [TSLP] from alarmins), neuropeptide receptors, and opioid receptors. Various drugs, particularly beta-lactam antibiotics and monoclonal antibodies, can trigger "IgE-dependent mast cell activation" via drug-specific IgE antibodies. However, mast cell degranulation in these patients can also occur through IgE-independent mechanisms, independent of FcεRI-IgE complex cross-linking (14).

Recent studies have shown that the Mas-related G protein-coupled receptor X2 (MRGPRX2), a receptor expressed in human mast cells with functional properties, plays an important role in the pathogenesis of drug hypersensitivity reactions not mediated by IgE. This finding has contributed to a better understanding of FcεRI-independent mast cell activation mechanisms. MRGPRX2 is a surface receptor sensitive to basic molecules and can be activated by various cationic pharmacological agents, leading to mast cell degranulation and the development of allergy-like inflammatory responses. In vitro mast cell studies have shown that this receptor can respond to agents such as vancomycin, fluoroquinolones, certain neuromuscular blockers (except succinylcholine), opioid analgesics (e.g., morphine), icatibant, and leuprolide. Additionally, natural peptides such as mastoparan, found in hornet and wasp venom, are also known to stimulate this receptor. It is thought that the range of agents capable of activating MRGPRX2 may be much broader than currently known (15). From a clinical perspective, it is difficult to distinguish MRGPRX2-mediated drug reactions from classical IgE-mediated hypersensitivity reactions. In reactions mediated by this receptor, positive responses obtained in skin tests with the responsible drugs are not diagnostically distinctive. Currently, there is no highly specific, definitive biomarker that can reliably indicate mast cell degranulation mediated by MRGPRX2 (16).

In a recent study, it was demonstrated that MRGPRX2 levels in the serum of patients with systemic mastocytosis were not significantly elevated. Although it has been reported that MRGPRX2 expression in mast cells in the skin of these patients is increased, this increase was found not to show a statistical correlation with disease burden, symptom severity, or serum tryptase concentrations. This finding suggests that the relationship between receptor expression and the clinical picture has not yet been clarified (17,18).

The management of drug-induced hypersensitivity reactions in mastocytosis and other mast cell-based diseases, along with uncertainties in diagnosis and treatment processes, poses a concerning situation for physicians following these patients. Concerns that the likelihood of a reaction developing may be "high" often lead to the adoption of "drug avoidance" strategies in clinical practice and to mislabeling of patients. However, this approach can have negative consequences, particularly in clinical situations requiring urgent intervention, such as infections, surgical procedures, invasive diagnostic procedures, or the COVID-19 pandemic, by limiting patients' timely and effective access to treatment. The aim of this review is to present current literature information on the diagnosis and management of allergies associated with medications, anesthetic agents, radiocontrast agents, and vaccines in patients with mastocytosis.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Drug hypersensitivity reactions to NSAIDs are the second most commonly reported cause of drug hypersensitivity in the general population after antibiotics. It has been suggested that the incidence and severity of NSAID-

induced HR may be increased in individuals with mastocytosis. In the current literature, there are limited studies that comprehensively evaluate the frequency, clinical characteristics, and course of NSAID-related DHR in patients with mastocytosis. The frequency of NSAID hypersensitivity in patients with mastocytosis ranges from 2% to 14% (19,20).

In a retrospective cohort study involving 388 adult patients from two European mastocytosis centers in Sweden and Italy, the prevalence of NSAID-related hypersensitivity reactions was determined to be 11.3%. The majority of patients (89%) presented with skin-limited symptoms, and severe systemic reactions were rarely observed. Anaphylactic reactions were reported in only 11 patients (2.8%). Notably, all NSAID-related hypersnsitivity reactions occurred before the diagnosis of mastocytosis was made. Additionally, no significant differences were found between NSAID-reactive and non-reactive patients in terms of gender distribution, baseline serum tryptase levels, atopy, or the presence of concomitant asthma/rhinitis. In the study reported in Spain and Italy, acetylsalicylic acid (ASA) was the primary trigger, while in Sweden, diclofenac was more frequently identified as the responsible drug (1,21) .This study shows that the incidence of hypersensitivity reactions to NSAIDs in individuals with systemic mastocytosis is approximately four times higher than in the general population. However, the majority of reactions were limited to skin-specific symptoms, and systemic anaphylactic responses were rarely detected. The data obtained suggest that patients diagnosed with mastocytosis who have previously used NSAIDs without issues can safely continue to use these medications without additional precautions. On the other hand, it emphasizes the need for a detailed allergic evaluation, including skin tests, in patients with a history of reactions to NSAIDs (21).

In a large retrospective study involving 418 adult and 223 pediatric patients with systemic mastocytosis, the tolerance of these patients to NSAIDs and other cyclooxygenase (COX) inhibitors was evaluated. Eighty-seven percent of adult patients and 91% of children demonstrated a clinically tolerable response to these pharmacological agents. Among individuals who developed reactions, the rate of adverse reactions to multiple NSAIDs was 5% in adults, while no such cases were observed in children (0%). In adults, the frequency of developing hypersensitivity reactions to two or more drugs has been found to be higher in women; in patients with a history of anaphylaxis triggered by agents other than NSAIDs, other COX inhibitors, and Hymenoptera venom; in those with baseline flushing; in individuals with a baseline serum tryptase level ≥48 ng/ml; and in patients carrying multilineage KIT mutations. On the other hand, tolerance to NSAIDs and other COX inhibitors appeared to be more common among male patients, those with a history of Hymenoptera venom-induced anaphylaxis, individuals with cutaneous manifestations of mastocytosis, and patients lacking baseline pruritus (20). The statistical findings suggest that the incidence of NSAID-induced hypersensitivity reactions among patients with systemic mastocytosis is lower than previously estimated. However, the inhibition of prostaglandin synthesis by NSAIDs is considered a potential mechanism that may contribute to the alleviation of mast cell-derived symptoms, particularly flushing (11).

In another retrospective study involving adult patients diagnosed with systemic and cutaneous mastocytosis, a loading protocol of up to 520 mg of ASA was administered to patients, and clinical responses were analyzed retrospectively. In this study, the incidence of NSAID-induced DHR was found to be 4.1%, and it was determined that the reactions in patients occurred before the diagnosis of mastocytosis. Only one of the 50 patients who underwent the loading test showed a positive response. This finding indicates that sensitivity to ASA is quite low in individuals with mastocytosis. NSAIDs, particularly ASA, may provide therapeutic benefit in controlling symptoms associated with mast cell activity by inhibiting prostaglandin D2 (PGD2) biosynthesis. This biochemical inhibition may contribute to alleviating clinical findings associated with excessive PGD2 release, such as flushing. Therefore, it is considered that NSAIDs can be used safely in individuals with mastocytosis in appropriate patients (19).

In the medical history, it is generally considered clinically safe to continue using the same drugs in patients who have used NSAIDs without complications in their medical history. However, in patients with a history of NSAID reactions, the results can be very serious and even fatal. Therefore, all NSAIDs (including parenteral forms such as ketorolac) should definitely not be used in these patients. It is recommended that such patients wear a medical alert bracelet (Medic-Alert) so that they can be easily identified by healthcare professionals in case of an emergency. While NSAIDs may continue to be used in patients who were able to use them without issues prior to receiving a diagnosis of mastocytosis, a risk-based approach should

be adopted in patients with unknown tolerance. If necessary, provocation tests should be planned under supervision for these patients. In patients with a low-risk profile, targeted NSAIDs are tested in a controlled environment to assess safety, while in high-risk cases, it is recommended to try selective COX-2 inhibitors such as celecoxib under observation. Many mastocytosis patients with NSAID intolerance can use alternative pharmacological options such as paracetamol (acetaminophen), COX-2 selective agents, and meloxicam without issues. However, in patients with a history of hypersensitivity to NSAIDs or those who have developed new reactions, a detailed allergic evaluation should be performed. This evaluation should be conducted by an experienced allergy-immunology specialist, with potential risks and benefits assessed in collaboration with the patient, and the decision-making process should be carried out. This approach is of great clinical importance in terms of both ensuring patient safety and preventing unnecessary drug restrictions (1,11,22). In a study, a risk analysis classification was performed, and it was found that the high-risk group for reactions associated with mast cell mediator release due to COX inhibitors in patients with systemic mastocytosis included female gender, presence of flushing, serum tryptase levels above 48 ng/mL, and patients with multilineage KIT mutations; while the low-risk group was characterized by male gender, presence of skin lesions, history of anaphylaxis due to Hymenoptera venom, and absence of itching (20).

ANTIBIOTICS

Antibiotics are among the most common etiological agents of DHR. The prevalence of antibiotic-related hypersensitivity in the general population ranges from 10% to 20%. Among this class of drugs, beta-lactam antibiotics are particularly notable for being the most frequently implicated in hypersensitivity reactions globally. This is largely attributed to their broad-spectrum activity and extensive use in both outpatient and inpatient settings, making them one of the most commonly prescribed antibiotic groups in primary care (1).

In individuals diagnosed with systemic mastocytosis, the risk of developing antibiotic-related hypersensitivity reactions is reported to be higher than in the general population. In this patient group, serious adverse immune responses and hypersensitivity reactions have been observed to various classes of antibiotics, including beta-lactams, quinolones, and vancomycin (11).

In a 15-year retrospective study involving 239 adult patients with systemic mastocytosis, all patients underwent a comprehensive allergic evaluation, and reported antibiotic-related reactions were individually analyzed by an allergy specialist. In this study, antibiotic-related hypersensitivity reactions were confirmed in 14.2% of patients, with the majority of cases limited to cutaneous symptoms and anaphylaxis observed in only 0.8% of cases. The most commonly reported triggers were beta-lactam antibiotics; however, no significant differences were found between individuals who developed hypersensitivity and those who did not in terms of age, gender, atopic status, and baseline serum tryptase levels. These data indicate that the prevalence of antibiotic-related hypersensitivity in mastocytosis patients is similar to that in the general population and that antibiotics rarely cause serious reactions in this patient group. Based on these findings, it is suggested that mastocytosis patients without a history of hypersensitivity to antibiotics can be treated without special precautions (23).

In a study involving 133 pediatric cases diagnosed with cutaneous mastocytosis, hypersensitivity reactions to beta-lactam antibiotics developed in 4.5% of pediatric patients (24). These findings suggest that the frequency and severity of antibiotic-related allergic reactions may vary depending on the subtype of the disease (cutaneous or systemic mastocytosis) and age group (pediatric or adult population). To better understand these differences, more comprehensive studies incorporating prospective subgroup analyses are needed.

It has been suggested that acute DHR may arise not only through IgE-mediated classical allergic mechanisms but also through IgE-independent alternative pathways. In a study involving quinolone antibiotics, quinolone-specific IgE was detected in 54.5% of cases that exhibited a reaction(25). However, this finding has not been supported by other studies. In subsequent studies, it has been suggested that non-IgE mast cell activation, particularly via MRGPRX2, may be the fundamental pathophysiological mechanism underlying reactions to these drugs. As mentioned earlier, MRGPRX2 is a G-protein-coupled receptor that is highly expressed in skin mast cells. Increased expression levels of this receptor have been demonstrated in conditions such as urticaria and cutaneous mastocytosis. MRGPRX2 can interact with positively charged (basic) drugs such as neuromuscular blocking agents, vancomycin, and quinolones to trigger mast cell degranulation without using the classical IgE pathway (11). Due to the unpredict-

able nature of reactions mediated via MRGPRX2 and the lack of diagnostic tests specific to this mechanism for routine clinical use, it has been recommended that the use of basic compound drugs such as quinolones and vancomycin should be limited as much as possible in patients with mastocytosis. When the use of these agents is unavoidable, slow infusion protocols and appropriate premedication strategies are recommended to reduce the risk of adverse reactions (1).

In the evaluation of drug hypersensitivity reactions (DHR) in patients with mastocytosis, it is recommended to utilize diagnostic methods with high sensitivity and specificity. Skin tests performed with well-characterized drugs such as penicillin, measurement of drug-specific IgE levels in serum, and in vitro approaches such as the basophil activation test (BAT) can all contribute to the diagnostic process.

As mentioned above, especially vancomycin and quinolones may cause mast cell activation through non-IgE pathways via MRGPRX2 rather than classical IgE-mediated mechanisms. When administration of these agents is necessary, vancomycin should be infused using a slow infusion protocol, while quinolones can be administered with appropriate premedication and under close monitoring. For other antibiotic groups, testing under observation is not mandatory.

In conclusion, antibiotics used without any problems before the diagnosis of mastocytosis are considered safe to be used again when clinically necessary. Re-examination for allergy to these drugs is usually not considered necessary. On the other hand, in patients with the possibility of DHR, it is recommended that they be assessed at specialized centers to ensure appropriate diagnostic management. The diagnostic approaches followed in such cases are the same as those used in the general patient population.

PERIOPERATIVE MEDICATIONS

Perioperative anaphylaxis is a sudden onset and potentially life-threatening hypersensitivity that can be triggered by the simultaneous administration of multiple pharmacologic agents such as local and general anesthetics, opioids, neuromuscular blocking agents (NMBAs). Other substances involved, such as antibiotics, colloid solutions, contrast agents, chlorhexidine and latex, may also contribute to these reactions. Patients with a diagnosis of systemic mastocytosis are considered to be at an increased risk of perioperative reactions. The main mechanism underlying the increased susceptibility is the concomitant use of drugs with the potential to trigger non-specific mast cell degranulation, such as NMBAs, opioids, ketamine, propofol. The effects of these drugs are thought to be mediated through the MRGPRX2 receptor, which is highly expressed especially in cutaneous mast cells (1).

Local anesthetics (LAs) may cause post-administration reactions by various mechanisms, including toxic and vasovagal effects, physiological changes due to co-administration with epinephrine, and true allergic reactions. The incidence of these reactions is reported in the literature with rates ranging from 2.5% to 10%. Although the development of amide-derived local anesthetics has contributed to a decrease in hypersensitivity events, the actual prevalence of allergic reactions due to these agents is not clearly known. The rates reported in different studies vary between 0% and 5% (26).

In a comprehensive retrospective analysis, 432 adult patients with suspected systemic mastocytosis were evaluated. Since LAs should be administered to these patients prior to bone marrow biopsy, skin prick test (SPT), intradermal test (IDT) and subcutaneous provocation tests with LAs were performed in individuals with a positive prior drug history, multiple drug intolerance or severe hypersensitivity reactions, respectively. The findings revealed that the risk of confirmed hypersensitivity reactions to LAs in patients with systemic mastocytosis was extremely low and did not differ significantly compared with the general population (26).

In a retrospective study conducted by the Spanish REMA network, 35 of 45 women diagnosed with indolent systemic mastocytosis (ISM) during pregnancy underwent epidural or local anesthesia and only 5 of these patients showed mild hypersensitivity symptoms such as pruritus, erythema and flushing. In this context, it has been concluded that local anesthetics can be safely administered to patients with mastocytosis when clinically indicated (27).

Among NMBAs, atracurium and mivacurium have been shown to cause allergic reactions more frequently. In contrast, agents such as pancuronium and cis-atracurium are generally considered safer. This difference is thought to be due to non-IgE mast cell stimulation through a receptor called MRGPRX2. True IgE-mediated allergic reactions to drugs in the opioid group are extremely rare; most reactions occur by mechanisms that directly stimulate mast

cells but are not allergic. According to studies, synthetic opioids (fentanyl, sufentanil, remifentanil and alfentanil) are considered lower risk than natural opioids such as morphine and codeine because they cause less tryptase release from mast cells in the skin (1).

The safety of pharmacological agents used in general anesthesia in individuals with mastocytosis has been examined in detail in various studies. In this context, in a large-scale retrospective analysis including 501 patients, it was reported that 2% of adult patients developed DHR and 0.4% developed anaphylaxis. In the pediatric subgroup of the same study, the incidence of DHR was 4% and anaphylaxis was 2%. Although these data reveal that the risk of hypersensitivity to perioperative drugs is statistically significantly increased in patients with mastocytosis, it has also been shown in the literature that the same anesthetic agents can be safely tolerated with appropriate premedication protocols (27). In patients with mastocytosis, previous general anesthesia applications and tolerance status to the agents used must be questioned during the pre-anesthetic evaluation process. In patients with a history of adverse reactions in the past, investigation of tolerance to alternative drugs will be guiding in terms of safe agent selection in future surgical or interventional procedures. In the evaluation of perioperative anaphylaxis, if all diagnostic tests are negative and possible allergens are excluded, the possibility of mastocytosis should be kept in mind even if the baseline serum tryptase level is within normal limits. Prophylactic medication with H1 and H2 receptor blockers, systemic corticosteroids and montelukast may be considered based on patient-based risk assessment (1). The use of premedication should be strongly considered, especially in certain patient groups. The possible protective effect of premedication should be considered in individuals with a previous history of severe anaphylactic reactions, in patients with elevated mast cell activity (e.g., elevated serum tryptase levels or diffuse mast cell infiltration), and in patients who have developed perioperative hypersensitivity reactions during previous surgical or interventional procedures (11). In addition, physical stimuli that may trigger perioperative mast cell activation, especially extreme temperature changes, prolonged operations and mechanical stress, should be limited or avoided as much as possible (1).

RADIOLOGIC CONTRAST AGENTS (RCM)

Radiocontrast agents (RCMs) are widely used in imaging techniques and adverse reactions due to these agents are extremely rare in the general population, with a reported incidence of less than 1%. IgE-mediated and non-IgE-mediated mechanisms play a role in the pathogenesis of reactions to RCM. Although it is estimated that reactions to RCM in SM patients may occur due to mast cell degranulation, there is no significantly increased risk in SM patients compared to the general population (1).

There are several case reports of mast cell activation due to RCM in patients with mastocytosis. In these cases, reactions ranging from mild to severe, including anaphylaxis, have been described. In a study; 120 cases of anaphylaxis, RCM was reported to be the triggering agent in only two cases (8). However, in another series of 220 RCM hypersensitivity cases, no individual with clonal mast cell disease was found (28). In an Italian study, only 8.1% of 86 patients with a history of drug or food-induced anaphylaxis had a baseline serum tryptase level >11.4 ng/mL and only one of these patients showed sensitization to RCM; however, the diagnosis of clonal mast cell disease was not confirmed in this individual (29). In a multicenter study conducted in Europe, no case of systemic mastocytosis was diagnosed among patients with a history of RCM-induced hypersensitivity.

In the light of the available data, it is not possible to conclude that RCM-induced anaphylaxis is more frequent in individuals with mastocytosis compared to the general population. There is no standard premedication protocol for the administration of radiologic contrast media (RCM) in mastocytosis patients with a history of drug-induced anaphylaxis. However, considering that RCMs can rarely cause severe and potentially fatal reactions even in the general population, these agents should be used carefully in individuals with mastocytosis. If necessary, standard premedication for the general population should be administered before RCM, healthcare personnel should be informed about potential risks, and emergency intervention equipment should be readily available (22). The combination of non-sedative second-generation antihistamines and systemic corticosteroids is one of the protocols widely recommended for premedication and frequently preferred in clinical practice (11).

VACCINES

Vaccine safety studies in individuals with mastocytosis are mostly based on retrospective patient data. These data suggest that the incidence of adverse reactions to vaccines may be increased in patients with mastocytosis compared

to the general population (11). Our experience with vaccine reactions in patients with mastocytosis has increased mainly after the rise in vaccinations during the COVID-19 pandemic.

The largest study conducted in the context of COVID-19 vaccination evaluated 323 patients who received a total of 666 vaccine doses. Vaccine administration was generally well tolerated, with only 6% (40 patients) reporting symptoms after a total of 666 doses of vaccine. The most common reactions were cutaneous symptoms (itching, urticaria, flushing), gastrointestinal symptoms, respiratory complaints and rarely musculoskeletal complaints. In 6 patients, reactions involving more than one organ system were observed; these cases were evaluated according to Brighton anaphylaxis criteria. Only a single patient fulfilled the Brighton Level 1 criteria for anaphylaxis, the remaining cases were categorized under lower diagnostic levels. The majority of reactions affecting multiple systems occurred after the first dose and particularly following the Pfizer-BioNTech vaccine. Adrenaline was administered to two patients, and it was noted that one of them had not been on their regular antihistamine treatment and had not received premedication before vaccination. A significant proportion of patients (80.2%) used H1-antihistamines and three patients were additionally premedicated with systemic corticosteroids. However, there was no statistically significant difference in the frequency of adverse reactions between those who received premedication and those who did not. Furthermore, since many patients were under chronic antihistamine treatment for mast cell activation disorders, this was not considered as premedication. In patients with hereditary alpha-tryptasemia (HαT), no significant difference in the frequency of adverse reactions due to genotype was observed (30).

CONCLUSION

Patients with mastocytosis can develop drug-induced anaphylactic reactions; however, the incidence of such reactions is lower compared to anaphylaxis caused by Hymenoptera venom. In the literature, anaphylactic reactions triggered by many different pharmacologic agents including anesthetic agents, RCMs, antibiotics, NSAIDs, codeine and other opioid derivatives have been described in this patient group (22).

Therefore, it should be kept in mind that underlying systemic mast cell disease may be present in all individuals who develop anaphylaxis. During clinical evaluation, comparison of serum tryptase levels both during the acute reaction when possible and at baseline, and a detailed dermatologic examination will contribute to the diagnostic process. Furthermore, mastocytosis patients with a history of drug-induced anaphylaxis should be considered to be at increased risk for re-reaction and should be referred for further evaluation by allergists.

Accurate identification and classification of hypersensitivity reactions is extremely important both to minimize the risk of anaphylaxis and to prevent unnecessary drug restrictions for these patients. Premedication strategies are recommended especially in high-risk individuals, and patients with a history of adverse reactions should undergo a comprehensive allergy evaluation. In this assessment process, correction of allergy mislabeling (delabeling) and the use of objective testing methods increase patients' access to effective and safe treatment options, positively affecting treatment success and quality of life.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Authorship Contributions

Concept: **Aytül Zerrin Sin,** Design: **Nihal Mete Gökmen, Aytül Zerrin Sin,** Data collection or processing: **Eda Aslan,** Analysis or Interpretation: **Eda Aslan, Nihal Mete Gökmen, Aytül Zerrin Sin,** Literature search: **Eda Aslan,** Writing: **Eda Aslan, Nihal Mete Gökmen, Aytül Zerrin Sin,** Approval: **Aytül Zerrin Sin.**

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