Mastocytosis and Allergic Diseases

P Bonadonna,[1] C Lombardo,[1] R Zanotti[2]

[1]Allergy Unit, Azienda Ospedaliera Universitaria Integrata Verona, Piazzale Stefani, Verona, Italy
[2]Department of Medicine, Section of Hematology, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy

Abstract

Mastocytosis is a clonal disorder characterized by proliferation and accumulation of mast cells in various tissues, mainly skin and bone marrow. It can cause a wide variety of clinical manifestations—other than urticaria pigmentosa—that can lead to inappropriate release of mediators by mast cells. The most severe manifestation is anaphylaxis.

The triggers of anaphylaxis in adults with mastocytosis are numerous, but Hymenoptera stings seem to be the most frequent, followed by foods and drugs.

Therefore, to prevent severe reactions, it is very important to recognize and avoid potential triggers; in addition, venom-allergic patients must receive lifelong immunotherapy, which has proven very effective.

Given that published data on drug anaphylaxis in patients with mast cell disorders are scarce, it is not currently possible to provide clear recommendations.

The risk of systemic reactions during general anesthesia can be reduced by assessing risk on an individual basis (previous reaction to a drug or reaction during surgery) and by avoiding specific trigger factors (patient temperature changes, infusion of cold solution, tissue trauma, friction, and other mechanical factors).

Key words: Clonal mast cell diseases. Anaphylaxis. Tryptase. Drug allergy. Hymenoptera venom allergy. REMA score. Immunotherapy.

Resumen

La mastocitosis es una enfermedad clonal caracterizada por la proliferación y acúmulo de mastocitos (MC) en diferentes tejidos, sobre todo en la piel y en la médula ósea (MO), que da lugar a una amplia variedad de manifestaciones clínicas, entre ellas la urticaria pigmentosa, siempre debidas a la inapropiada liberación de mediadores de MC, siendo la más grave de ellas la anafilaxia.

Los desencadenantes de la anafilaxia en adultos con mastocitosis son numerosos, pero la picadura de himenópteros parece ser la más frecuente, seguida de algunos alimentos y medicamentos.

En la prevención de las reacciones graves es muy importante reconocer y evitar el posible agente desencadenante, siendo también importante que los pacientes con alergia a venenos sigan un tratamiento largo con inmunoterapia que se ha demostrado efectivo en dichos pacientes.

Los datos publicados sobre anafilaxia por medicamentos en pacientes con mastocitosis son escasos y no es posible dar unas claras recomendaciones sobre este tema.

El riesgo de reacciones sistémicas durante la anestesia general puede reducirse haciendo un seguimiento de los riesgos personales de cada paciente (con reacciones previas a medicamentos o durante una cirugía), y evitando los factores desencadenantes (cambios de temperatura, infusión con soluciones frías, fricción y otros agentes mecánicos.

Palabras clave: Enfermedades clonales mastocitarias. Anafilaxia. Triptasa. Alergia a medicamentos. Alergia a veneno de himenópteros. Score REMA. Inmunoterapia.

Introduction

The term mastocytosis encompasses a heterogeneous group of clonal disorders characterized by proliferation and accumulation of mast cells (MCs) in various tissues, mainly skin and bone marrow [1]. Cutaneous mastocytosis is most frequent in childhood, while systemic mastocytosis mainly affects adults and involves 1 or more extracutaneous organs (bone marrow, gastrointestinal tract, lymph nodes, and spleen), with or without skin involvement. Most cases of systemic mastocytosis involve a somatic autoactivating point mutation at codon 816 of the kit-receptor gene [2]. Mastocytosis has a wide variety of clinical manifestations other than typical skin lesions (eg, pruritus, urticaria, angioedema, flushing, nausea, vomiting, abdominal pain, diarrhea, anaphylaxis, and osteopenia/osteoporosis), and these are always caused by the inappropriate release of mediators by MCs. In rare cases of aggressive disease, the clinical features are related to end-organ dysfunction due to tissue infiltration by MCs (eg, hypersplenism, pathologic bone fracture, ascites, malabsorption, and cytopenia) [3].

Recent studies estimated that the prevalence of systemic mastocytosis in European adults is approximately 1.0-1.3 cases per 10 000 inhabitants [4-6]. Mastocytosis can affect any age group, and gender distribution is approximately equal [7]. In most cases, mastocytosis is sporadic, although familial clusters have been reported [8,9].

The diagnosis and classification of mastocytosis are based on the identification of neoplastic MCs by their morphological, immunophenotypic, and molecular characteristics based on well-established World Health Organization (WHO) criteria (Table 1) [1].

The WHO classification defines 7 variants of mastocytosis: cutaneous mastocytosis, indolent systemic mastocytosis (ISM), systemic mastocytosis with an associated clonal hematologic non-MC lineage disease, aggressive systemic mastocytosis, MC leukemia, MC sarcoma, and extracutaneous mastocytoma. To subclassify systemic mastocytosis, criteria associated with MC burden (B findings) or aggressiveness of disease (C findings) are also applied (Table 1). The term *monoclonal MC activation syndrome* (MMAS) has been proposed to identify patients with unexplained or recurrent anaphylaxis without skin lesions who do not fulfill the previously mentioned criteria for systemic mastocytosis but are shown to have documented markers of MC clonality [10].

Serum Tryptase Level

Tryptase is contained in the secretory granules of human MCs and has trypsin-like activity. Since it is produced almost exclusively by MCs, with the exception of a small amount produced by basophils, it is considered the marker of MC disorders.

Measurement of serum tryptase is based on immunometric methods. In most laboratories, the upper normal value is 11.4 ng/mL. Patients with cutaneous mastocytosis have normal or only mildly elevated serum tryptase. In the early stages of

Table 1. WHO Diagnostic Criteria for Systemic Mastocytosis

A firm diagnosis of systemic mastocytosis is established when at least 1 major and 1 minor or at least 3 minor criteria are present	
Major	Multifocal dense infiltrates of MCs in bone marrow sections or other extracutaneous organs (>15 MCs in aggregate).
Minor	a. MCs in bone marrow or other extracutaneous organs show an abnormal (spindle-shaped) morphology (>25%). b. Mutation at codon 816 of the *KIT* gene in extracutaneous organs. In most cases the mutation is D816V. c. MCs in bone marrow express CD2 and/or CD25. d. Serum tryptase >20 ng/mL (not in patients with AHNMD-type disease).
B findings	a. Bone marrow biopsy showing >30% infiltration by MCs (focal, dense aggregates) and/or serum tryptase level >200 ng/mL. b. Signs of dysplasia or myeloproliferation in non-MC lineages, but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or slightly abnormal blood counts. c. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.
C findings	a. Bone marrow dysfunction manifesting as cytopenia (ANC <1.0 x 10^9/L, Hb <10 g/dL, or platelets <100 x 10^9/L), but no obvious non-MC hematopoietic malignancy. b. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension. c. Skeletal involvement with large osteolytic lesions and/or pathological fractures. d. Palpable splenomegaly with hypersplenism. e. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates.

Abbreviations: AHNMD, associated clonal hematologic non–mast cell lineage disease; ANC, absolute neutrophil count; Hb, hemoglobin; MC, mast cell.
Diagnosis of:
(a) Indolent SM (ISM): meets criteria for SM. No C findings. No evidence of AHNMD.
(b) Smoldering SM: as ISM, but with 2 or more B findings and no C findings.
(c) Isolated bone marrow mastocytosis: as ISM with bone marrow involvement, but without skin involvement.
(d) Aggressive SM: meets criteria for SM. One or more C findings. No evidence of mast cell leukemia.
(e) Mast cell leukemia: meets criteria for SM. Bone marrow biopsy shows a diffuse infiltration, usually compact, by atypical, immature mast cells. Bone marrow aspirate smears show ≥20% mast cells. In typical mast cell leukemia, mast cells account for ≥10% of peripheral white blood cells.

systemic mastocytosis, serum tryptase levels may be normal, increase over a period of months or years, and then remain stable, without progressing to a more aggressive form of the disease. The serum tryptase concentration usually correlates with the MC burden, except in patients who develop diffuse bone sclerosis, although it is not directly related to MC burden [11,12].

Elevated serum tryptase levels are not specific to mastocytosis. Transiently elevated levels can be found in other forms of severe anaphylaxis with hypotension, hematologic malignancies of myeloid origin, and nonneoplastic conditions such as end-stage chronic renal failure, onchocerciasis, and chronic urticaria [13,14].

Diagnosis of Systemic Mastocytosis

The diagnosis of systemic mastocytosis is based on major criteria (histological finding of at least 15 multifocal dense MC infiltrates in bone marrow or other extracutaneous organs) plus 1 minor criterion, or on 3 minor criteria (abnormal morphology of extracutaneous MCs, serum tryptase >20 ng/mL, expression of CD2 and/or CD25 on bone marrow MCs, and detection of a mutation at codon 816 of the *KIT* gene in extracutaneous organs) [1]. The major histological criterion is often not met, since only small clusters or isolated scattered MCs are detectable in bone marrow. In such cases, other sensitive tests are needed to confirm the diagnosis of systemic mastocytosis, namely, flow cytometry, which can demonstrate aberrant expression of CD25 or CD2 in bone marrow MCs (even in cases with a low MC burden), and identification of a mutation at codon 816 of the *KIT* gene using reverse-transcriptase polymerase chain reaction (RT-PCR) with restriction fragment length polymorphism, peptide nucleic acid PCR, allele-specific PCR, and quantitative RT-PCR [3,15,16].

Systemic Mastocytosis and Allergic Diseases

The prevalence of atopy in patients with mastocytosis does not differ from that of the healthy population, as shown in 3 large studies [17-19], although the incidence of anaphylaxis is higher in mastocytosis. The cumulative prevalence of anaphylaxis in patients with mastocytosis has been reported to range between 22% and 49% in adults and 6% and 9% in children [17-19].

The triggers that induce massive degranulation of MC and cause anaphylaxis in adults with mastocytosis are numerous, although Hymenoptera stings seem to be the most frequent (19-53% of cases of anaphylaxis), followed by foods (3-16%) and drugs (5-9%) [17-19]. Alcohol, exercise, and temperature changes are also potential triggers of anaphylaxis in patients with systemic mastocytosis, although they act mainly as cofactors. A study involving 120 patients (both adults and children) showed that 26% of reactions in adults occur only after a combination of triggers [18], as previously reported in patients without mastocytosis [20]. Idiopathic anaphylaxis is not as rare (39% of cases of anaphylaxis) in systemic mastocytosis [19]. Identification of potential triggers is therefore key to ensuring appropriate avoidance and reduction of risks.

Fatal anaphylaxis may be either idiopathic or caused by hymenoptera stings. It can also occur during the postsurgical period and after the intake of drugs (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] and opiates) and foods [18,21-25]. Of note, vasoconstriction-related features, such as increased blood pressure, are occasionally observed in some patients during acute episodes of MC activation [18]. Finally, neurological ischemic symptoms suggesting transient cerebral vasospasm (2 patients) and a case series of Kounis syndrome have been reported [26-28].

Anaphylaxis is often a manifestation of mastocytosis, particularly in patients with systemic mastocytosis and other clonal MC disorders such as MMAS without skin lesions. A predictive model for clonal MC disorders based on clinical and laboratory findings was proposed by Alvarez-Twose et al [29] (Table 2). A Spanish Network on Mastocytosis (Red Española de Mastocitosis [REMA]) score ≥2 can predict the presence of clonal MCs or systemic mastocytosis in patients who experience anaphylaxis without cutaneous mastocytosis with a sensitivity of 92% and a specificity of 81% [29].

Table 2. REMA Scoring Model[a]

Variable		Score
Gender	Male	+1
	Female	–1
Clinical symptoms	Absence of urticaria and angioedema	+1
	Urticaria and/or angioedema	–2
	Presyncope and/or syncope	+3
Serum tryptase	<15 ng/mL	–1
	>25 ng/mL	+2

Abbreviation: REMA, Red Española de Mastocitosis (Spanish Network on Mastocytosis).
[a]Proposed as a screening method for the presence of clonal mast cells in patients presenting with anaphylaxis in the absence of cutaneous mastocytosis before a bone marrow study.

Hymenoptera Venom Allergy and Systemic Mastocytosis

Epidemiology

The literature consistently confirms a preferential association between hymenoptera venom allergy (HVA) and mastocytosis [30]. The prevalence of HVA in the adult general population in Western countries is about 3%, whereas the prevalence of insect venom allergy in patients with any form of mastocytosis is higher, about 20-30% [10,31,32]. Furthermore, patients with systemic mastocytosis and HVA have a greater risk of severe systemic reactions than patients without systemic mastocytosis, as described in several case reports and small series of patients with HVA [22,33-36]. The prevalence of systemic mastocytosis in the general population is 1.0-1.3 cases per 10 000 inhabitants, although the prevalence of systemic mastocytosis in patients with HVA is significantly higher (Table 3) [30]. The first report on evaluation of bone marrow

Table 3. Prevalence of Clonal Mast Cell Disease in Patients With Systemic Reactions to Hymenoptera Venom Screened on the Basis of Elevated Tryptase

Author	Patients	Elevated Tryptase, No. %	Clonal Mast Cell Disease	%
Haeberli et al 2003[a] [69]	259	19 (7.3)	3 CM	1%
Dubois 2004[b] [47]	2375	32 (1.3)	22 SM	1%
Rueff et al 2006[c] [71]	1102	106 (9.6)	21 CM + 8 SM	2.6%
Bonadonna et al 2009 [24]	379	44 (11.6)	21 ISM + 9 MMAS	7.9%
Potier et al 2009[c] [72]	138	22 (15.9)	1 CM + 5 SM	4.4%
Guevara et al 2010[c,d] [73]	274	30 (10.9)	1 CM + 3 ISM	1.5%

Abbreviations: CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; MMAS, monoclonal MC activation syndrome; SM, systemic mastocytosis.
[a]Bone marrow evaluation not performed.
[b]Screening with urinary histamine metabolite.
[c]Evaluation of CD25/CD2 mast cell coexpression and *KIT* mutation not performed or reported.
[d]Bone marrow evaluation performed if serum tryptase >15 ng/mL.

in patients with HVA and elevated tryptase, including detection of minor criteria for mastocytosis, showed the frequency of clonal MC disorder to be as high as 7.9% [24].

The association between high rates of anaphylaxis and mastocytosis was initially observed in patients with urticaria pigmentosa, although there is increasing evidence that anaphylaxis is more common in patients with systemic mastocytosis and no skin involvement [1,30]. The risk of anaphylaxis seems to increase as serum tryptase levels increase, since a higher mast cell burden can lead to spontaneous MC degranulation [35]. Unexpectedly, HVA-induced anaphylaxis is rare in patients with aggressive subtypes of systemic mastocytosis, who harbor the highest MC burden [36,37]. This observation might lead us to question the fact that the risk of HVA increases with increasing MC burden. In fact, the highest prevalence (50%) was found in patients with ISM and tryptase levels ranging from 20.4 µg/L to 29.9 µg/L, whereas in mastocytosis patients with levels below 6.1 µg/L and above 191 µg/L the prevalence of HVA was under 10% [36]. A recent study of 335 patients with MMAS showed that ISM without skin lesions associated with insect-induced anaphylaxis had clinical and biological features that were significantly different from those of other forms of ISM and were associated with good prognosis [38]. Compared with patients who have other types of ISM, these patients are mainly males with a low frequency of mediator-related symptoms and lower median baseline serum tryptase levels. Moreover, they less frequently have bone marrow MC aggregates and systematically harbor MC-restricted *KIT* mutations. Nonetheless, as shown in Table 4 (unpublished personal case series), osteoporosis, which is sometimes associated with vertebral fractures, affected 30% of 145 patients diagnosed as having clonal MC disorders with HVA as the presenting symptom at our multidisciplinary outpatient clinic. This frequency is similar to that reported in other types of ISM. In our experience, the diagnosis of a previously undetected cutaneous mastocytosis is not infrequent in these patients.

Routine determination of serum tryptase and application of the REMA score is strongly recommended during

Table 4. Clinical, Laboratory, and Bone Marrow Evaluation Results of 145 Patients With Systemic Reaction After Hymenoptera Sting[a]

	MMAS	ISM Without CM	ISM With CM
Male sex, No. (%)	10 (91)	83 (72)	13 (65)
Median (range) age, y	56 (25-79)	56 (19-77)	52 (19-69)
Mueller grade IV, No. (%)	8 (73)	105 (91)	20 (100)
REMA score ≥2, No. (%)	8 (73)	104 (90)	18 (90)
Tryptase, ng/mL, median (range)	16 (12.7-32)	21 (11.6-134)	25 (11.8-142)
D816V positive, No. (%)	7 (64)	107 (96)[b]	20 (100)
Major WHO criterion fulfilled, No. (%)	0	33 (29)	10 (50)
Mast cells CD25/CD2 positive, No. (%)	0.001 (0-0.026)	0.045 (0.001-0.6)	0.035 (0.01-0.78)
Osteoporosis ± vertebral fracture, No. (%)	3 (27)	40 (35)	6 (30)
Total	11 (8%)	115 (78%)	20 (14%)

Abbreviations: CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; MMAS, monoclonal mast cell activation syndrome.
MIS= Mastocytosis in the skin
[a]Baseline serum tryptase >11.4 ng/mL and no cutaneous mastocytosis (diagnosis between 2006 and 2013 at the Multidisciplinary Outpatients Clinic for Mastocytosis, Verona, Italy).
[b]Four cases not tested.

the workup of patients with HVA in order to identify underlying clonal MC disorders. Given the typically low MC burden in bone marrow detected in most cases, and in order to avoid false-negative results, bone marrow studies should be carried out in reference centers for MC-related diseases, where highly sensitive techniques are routinely applied to study the bone marrow MC immunophenotype and molecular features (eg, *KIT* mutation) at the earliest stages of disease.

Diagnosis of HVA

Patients who experience anaphylactic reaction after hymenoptera sting should undergo diagnostic tests [39,40]. Skin testing can be performed as in patients without clonal MC disorders: skin prick tests are performed with the standard concentration of insect venom, ranging from 1 to 100 µg/L. If the results of skin prick tests are negative, intradermal tests should then be performed at concentrations of 0.001 to 1 µg/mL. Higher concentrations can lead to false-positive results [41]. Skin testing is usually safe. However, as it often involves insect venom and is thus a kind of allergen challenge, close medical supervision and immediate availability of resuscitation facilities are recommended (intravenous access and the possibility of immediate administration of epinephrine, fluids, oxygen, corticosteroids, and antihistamine drugs) [41,42].

Assays for Hymenoptera-specific IgE should be performed; if the result is negative, the test can easily be repeated and occasionally becomes positive few weeks later [43]. Skin testing and determination of specific IgE should be performed at least 4 weeks after the reaction. Some patients with mastocytosis may have negative results in the specific IgE assay and skin test. In a previous study, we found 4 patients with negative skin and serum test results for HVA, even though they had monoclonal mast cell disorders [24]. These patients generate a diagnostic dilemma, because the choice of extract to be used in cases of negative test results remains problematic and diagnostic sting challenge would not be ethical, since its negative predictive value is low. The basophil histamine release test could be a suitable diagnostic option in MC patients with negative skin test and IgE results [44].

Data on the basophil activation test (BAT) in patients with negative skin test and serum IgE results vary according to the center. The study by Bonadonna et al [41] showed that negative standard tests are reliable and that BAT did not add useful information. Other studies reported the usefulness of the method in false-negative patients with mastocytosis (sensitivity reaching 81-87%). Further studies are needed to confirm the usefulness of this test in patients with negative results [45,46].

Treatment of Patients With Hymenoptera Venom Allergy and Systemic Mastocytosis

Venom immunotherapy (VIT) is recognized as a life-saving treatment for patients with HVA. After some debate, mainly because of safety concerns, it is now generally accepted that VIT should always be administered [22,47]. It has also been suggested that VIT is safe and effective in patients with HVA and systemic mastocytosis [48,49].

Based on a large dataset, more robust recommendations were recently provided on the use of VIT in patients with systemic mastocytosis and HVA [50]. The authors confirmed VIT to be an effective and safe therapeutic option in this specific population. VIT was well tolerated, although slightly more adverse events were seen with the modified rush induction regimen. Therefore, even though statistical significance was not achieved, it would be reasonable to suggest a less aggressive induction pattern in patients with systemic mastocytosis. At variance with data from previous reports, the results showed that none of the patients discontinued treatment owing to VIT-related side effects and no reactions were observed during the maintenance period. Also of note, VIT conferred full protection in the vast majority of the study population, as observed in patients without systemic mastocytosis and in patients receiving an extended maintenance regimen [42,51,52]. Furthermore, in patients with HVA and systemic mastocytosis who were not fully protected at field re-sting, an increase in the maintenance dose to 200 µg was recommended [42].

Table 5. Effectiveness of Venom Immunotherapy (VIT) in Patients With Mastocytosis

Author	Time of Sting Challenge	No. of Patients	Patients With Systemic Reaction in Sting Challenge, No (%)	Patients With Systemic Reaction on Field Sting, No. (%)	Cumulative Number of Reactions to Re-sting
Rueff et al [71]	6-12 months after reaching maintenance dose	33	7/33 (21.6%)	–	7/33 (21.6%)
Dubois et al [47]	Not done	12		6/7 (85%)	6/7 (85%)
Bonadonna et al [24]	Not done	16	–	2/13 (15%)	2/13 (15%)
Haeberli et al [69]	3-5 years of VIT	10	4/10 (40%)	–	4/10 (40%)
Fricker et al [34]	Maintenance dose	10	0/3	1/3 (33%)	1/6 (16%)
De Olano et al [17]	Not done	21	–	3/12 (25%)	3/12 (25%)
Engler et al [70]	Not done	1		0/1	0/1
Bonadonna et al [42]	Not done	84	–	7/50 (14%)	7/50 (14%)
Total		187	11/46 (23.9%)	19/132 (20.0%)	30/132 (22.7%)

Overall, based on data from the literature (and considering the rarity of both conditions), the efficacy of VIT was fully evaluated in 187 patients with mastocytosis receiving VIT through sting challenges or field sting (Table 5). Patients with HVA and confirmed systemic mastocytosis should receive the appropriate VIT. This approach does not imply higher risk and confers effective protection against life-threatening systemic reactions.

No data have been reported on the long-term efficacy of VIT in patients with mastocytosis. However, 2 deaths have been reported in patients who were stung after discontinuing VIT [53].

Patients with mastocytosis who have experienced systemic reactions should carry 2 or more epinephrine autoinjectors. The same recommendation is appropriate for all VIT-treated patients with mastocytosis, even if they have reached the maintenance dose [54].

Drug Allergy and Mastocytosis

Drugs can trigger anaphylaxis in patients with mastocytosis. NSAIDs, β-lactam antibiotics, radiocontrast media, aminoglycosides, streptomycin, phenylephrine, codeine, and local and general anesthesia are listed as triggers in patient histories [17,18]. However, such reactions have not been confirmed by positive skin tests or provocation tests in the literature [55].

The frequency of underlying clonal MC disorders in patients with drug hypersensitivity is still unknown. In fact, few studies have tried to investigate undetected systemic mastocytosis in this population. An Italian study tried to determine the frequency of clonal MC disorders in patients with food- and drug-induced anaphylaxis by performing bone marrow biopsy in patients with increased serum tryptase levels (>11.4 ng/mL): only 1 out of 5 patients who underwent bone marrow testing was finally diagnosed with systemic mastocytosis. No cases of MMAS were documented. Moreover, the authors observed that the severity of the reactions was significantly greater in patients with drug hypersensitivity [56]. By contrast, in patients with HVA, 88% of those with anaphylaxis and elevated tryptase values did have systemic mastocytosis or MMAS, and the association between severe systemic reactions to drugs and mast cell disorders was low [24]. These data were subsequently confirmed in a study where the most common trigger for anaphylactic episodes in patients with clonal MC disorder was hymenoptera sting, whereas drugs were mostly involved as a trigger in nonclonal MC activation syndrome [29].

In other studies on hypersensitivity to anesthetics, which included serum tryptase measurements after reactions, bone marrow biopsy to diagnose clonal MC disorder was not performed [57,58].

Mastocytosis and General Anesthesia

Knowledge of perioperative drug safety in patients with mastocytosis is still scarce and based on case reports and small case series. Therefore, it is not possible to provide general recommendations regarding the tolerability/safety of drugs or drug families. Large cohort studies on the prevalence of reactions during general anesthesia in patients with systemic mastocytosis are needed. A recent review of the available literature on surgical procedures in mastocytosis patients tried to provide indications on perioperative management and avoidance of known triggers [59].

The risk of perioperative anaphylaxis in children with mastocytosis is low and limited to patients with extensive skin involvement (>40% of body surface) and high serum tryptase levels [18]. Equally effective drugs are available, but those with minimal histamine release (eg, fentanyl and vecuronium instead of morphine and atracurium or mivacurium) should be selected as in adults. Medication and equipment to treat perioperative anaphylaxis should be readily available [55]. The risk seems to be higher in adults and mainly in systemic forms such as ISM, regardless of skin involvement [18]. In adults, the risk is probably lower in patients who have never experienced anaphylaxis and/or have previously tolerated general anesthesia. Patients who have experienced anaphylaxis during anesthesia should be considered at higher risk. When possible, information on anesthetics tolerated in recent procedures should be obtained for all patients. The potential physical trigger factors to be avoided are sudden temperature changes in patients and in the operating room, infusion of cold solutions, widespread tissue trauma, friction, and other mechanical factors. Moreover, as mast cell degranulation can be triggered by anxiety, premedication with sedatives such as benzodiazepines should be considered in selected cases [55].

Table 6. Perioperative Drugs Associated With a Lower Risk of Reactions During Surgical Procedures in Mastocytosis

Drug Class							
Hypnotics	Benzodiazepine	Neuromuscular Blocking Agents	Anticholinergic	Halogenated Gases and Nitrous Oxide	Local Anesthetics	Opioids	Analgesics
Propofol	Midazolam	Pancuronium[a]	Atropine	Desflurane	Amide-type	Fentanyl	Paracetamol (acetaminophen)
Etomidate		Vecuronium[a]		Isoflurane		Sufentanil	
Ketamine		Cisatracurium[b]		Sevoflurane		Remifentanil	
				Nitrous oxide		Alfentanil	

[a]Non-depolarizing steroidal neuromuscular blocking agent.
[b]Non-depolarizing benzylisoquinoline neuromuscular blocking agent.

Information on anesthetics is shown in Table 6. Histamine-releasing drugs (ie, opiates and neuromuscular blocking agents) should be avoided if possible or administered slowly. Induction agents are generally well tolerated. Inhaled flurane anesthetics have not been associated with anaphylaxis [59,60]. Atracurium and mivacurium are the muscle relaxants with the most pronounced nonspecific histamine release. The highest number of allergic reactions has been reported for rocuronium and succinylcholine [60]. Vecuronium, pancuronium, and cisatracurium have not been reported to cause a high number of perioperative reactions. Opiates such as morphine and codeine should be avoided if possible, since they have been associated with mast cell activation in patients with mastocytosis. Fentanyl and related agents (remifentanil, sufentanil, and alfentanil) do not seem to carry a high risk of reactions [60]. The efficacy of premedication with antihistamines (anti-H1/anti-H2) or corticosteroids to prevent systemic reactions has not been confirmed. However, no evidence to the contrary has been reported: in fact, some specialists suggest premedication only in selected cases, whereas others recommend pretreatment in all patients in addition to chronic antimediator therapy [60,61].

Any regular maintenance medication taken to maintain mast cell stability and limit the effects of mast cell mediators should be continued during the operation.

Radiocontrast Media

Radiocontrast media have been reported to be a possible trigger for anaphylaxis in some case reports and in a few large studies [17,18,62,63]. Given the limited available data, it is not possible to compare the risk of anaphylactic reaction in patients with mastocytosis or MC activation syndrome who have been exposed to radiocontrast media with the risk in the general population.

No specific recommendations have been proposed for prevention of anaphylaxis in patients with mastocytosis and previous drug anaphylaxis, and the utility of this strategy has yet to be established [25,64]. Therefore, as radiocontrast media can induce severe—sometimes fatal—reactions in the general population (even nonionic media), it seems reasonable to adopt a cautious approach in patients with mastocytosis by administering premedication with antihistamines and corticosteroids in selected cases to prevent or reduce the severity of possible reactions. The medical team should be advised on how to manage possible severe reactions.

Other Drugs

Anaphylaxis can be triggered by antibiotics, especially β-lactams (amoxicillin, ampicillin, penicillin V) and aminoglycosides [17,18,65]. In one case report, a woman with high baseline levels of serum tryptase and suspected β-lactam allergy experienced anaphylaxis during skin testing with penicillin [66]. There are also reports of adverse reactions to NSAIDs in patients with mastocytosis [17,18]. In a recent cohort of 284 patients with reactions to NSAIDs, serum tryptase >20 ng/mL was not indicative of severe anaphylaxis, except for patients with HVA, suggesting that this population may receive NSAIDs without special precautions [67]. As in the general population, anaphylaxis can be triggered by cofactors (eg, aspirin and alcohol) in patients with MC disorders [68]. In general, only a small proportion of patients with mastocytosis develop adverse reactions to NSAIDs and antibiotics. Therefore, in patients who have never experienced adverse reactions to drugs, medications tolerated before and after the diagnosis are allowed. In contrast, in patients with a history of reactions to antibiotics, the culprit drugs and those belonging to the same antibiotic family should be avoided; in the case of reactions to NSAIDs, all drugs from this family should be strictly avoided. Moreover, patients should also wear a medical alert bracelet. Finally, it is very important to refer all patients with adverse reactions to drugs—especially patients with mastocytosis—to an allergy specialist for appropriate counseling and, if necessary, closely supervised testing (eg, skin test, provocation test).

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Conflicts of Interest

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Patrizia Bonadonna

Azienda Ospedaliera Universitaria Integrata Verona
Piazzale Stefani 1
37126 Verona, Italy
E-mail: patrizia.bonadonna@ospedaleuniverona.it

