

Mast Cell Diseases and Drug Hypersensitivity Reactions

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Opinion statement

Mastocytosis is a clonal disorder characterized by the proliferation and accumulation of mast cells (MCs) in different tissues, with a preferential localization in skin and bone marrow (BM). Patients with cutaneous and systemic mastocytosis could present symptoms, including immediate and severe hypersensitivity reactions, related to the increase of MC releasability and to the excess of mast cell in the tissues. Mastocytosis in adults is associated with a history of anaphylaxis in 22–49%. Hymenoptera stings represent the more frequent elicitor of anaphylaxis, sometimes fatal, in mastocytosis patients. Moreover, anaphylaxis after intake of drugs such as non-steroidal anti-inflammatory drugs, opioids and drugs in the perioperative setting is occasionally described in mastocytosis. However, data on the frequency of drug hypersensitivity in mastocytosis and vice versa are scarce and evidence for an association appears to be limited. Nevertheless, clonal MC disorders should be ruled out in cases of severe anaphylaxis based on the evaluation of basal serum tryptase determination, physical examination for cutaneous Mastocytosis lesions, and clinical characteristics of anaphylactic reaction. In this paper, we focused on the most relevant evidence about the association between mastocytosis and hypersensitivity to some classes of drugs. In addition, we tried to give recommendations, based on available literature data, about the use of these drugs in patients with diagnosed mastocytosis.

Introduction

Mastocytosis is a proliferative disorder of hematopoietic mast cell progenitors, leading to an expansion and accumulation of mast cells (MCs) in one or more organs, mainly skin, bone marrow (BM) and less frequently gastrointestinal tract, liver and spleen [1]. The prevalence of overt mastocytosis has been estimated to be about 0.9-1.3 per 10,000 inhabitants [2]. The prevalence of extra-cutaneous involvement in adults with mastocytosis is more than 90% with sensitive detection methods, leading to diagnosis of Systemic Mastocytosis (SM), whereas in children, the majority of patients have accumulations of MCs only in the skin (Cutaneous Mastocytosis, CM). The molecular basis of the disease is an activating mutation in the MC growth factor receptor KIT, a tyrosine kinase protein. About 90% of patients with SM carry a point mutation with exchange of aspartic acid to valine in codon 816 (D816V) [3, 4].

To diagnose SM, according to the World Health Organization (WHO), several criteria have to be fulfilled, including detection of mast cell aggregates, atypical MCs, aberrant CD25 expression by MCs, an activating mutation in *c-kit* in the BM or other extra-cutaneous tissue and serum tryptase levels >20 ng/ml (Table 1) [5]. SM is subdivided into different variants according to aggressiveness and prognosis, indolent SM (ISM) being the most common form. Other rare advanced forms are recognized in the WHO classification, recently revised: Smouldering SM (SSM), SM with an Associated Hematologic Neoplasia (SM-AHN), Aggressive SM (ASM), Mast Cell Leukemia (MCL) and Mast Cell Sarcoma (MCS) [6] (Table 2). CM is sub-classified into three variants (Table 2).

BM Mastocytosis (BMM) is a proposed sub-variant of ISM involving BM without skin lesions [1, 7–10]. Compared with other ISM, these patients are characterized by

male prevalence, lower median serum tryptase levels, lower MC burden, higher frequency of idiopathic and allergen-induced anaphylaxis with cardiovascular symptoms and lower occurrence of other mediator-related symptoms.

Patients that display mediator-related symptoms but not fulfill sufficient WHO criteria for SM, despite having KIT-mutated clonal MCs and/or BM MCs CD25 positive, are considered affected by the MC disorder, defined with various terms including (mono)clonal MC activation syndrome (MMAS) [7, 11–14] and clonal MC activation disorders [c-MCAD] [8, 9].

Anaphylaxis, one of the most common symptoms of mast cell disorders, is a generalized life-threatening systemic hypersensitivity reaction [15]. The studies available up to now confirmed that incidence and severity of anaphylaxis is greater in patients with mastocytosis compared to the general population [16–18]. In adults with mastocytosis, the cumulative prevalence of anaphylaxis has been reported to be between 22 to 49% of patients [14, 16, 18]. In children a significantly increased risk to develop anaphylaxis appears to be associated with extensive skin involvement and higher serum tryptase levels, [9, 16], especially during episodes of blistering [19].

The most common triggers that can determine a massive degranulation of MCs and cause anaphylaxis in adult subjects with mastocytosis are many, but the most frequent are hymenoptera stings (19-53%), foods (3-16%) and drugs (5-9%) [14, 16, 18]. Alcohol, exercise and temperature changes are other possible trigger factors of anaphylaxis, but they have been recognized to play roles not only as elicitors, but also as important co-factors in anaphylaxis.

Table 1. Diagnostic criteria for Systemic Mastocytosis (Horny et al. 2008)

The diagnosis of SM is established when at least one major and one minor or at least three minor criteria are present

Major	Multifocal dense infiltrates of MC in bone marrow sections or other extracutaneous organ(s) (>15 MCs in aggregate)
Minor	a. MC in bone marrow or other extracutaneous organ(s) show an abnormal (spindle-shaped) morphology (>25% of BM MCs) b. <i>KIT</i> mutation at codon 816 in extracutaneous organ(s). In the majority of cases, the mutation is D816V c. MC in bone marrow express CD25 d. Serum total tryptase >20 ng/ml (does not count in patients who have AHN)

Abbreviations: MC, mast cell(s), AHN, associated hematologic neoplasia

Table 2. WHO classification of mastocytosis (Horny et al. 2008, Arber et al. 2016)

Cutaneous Mastocytosis (CM)	<i>variants</i> Maculo-Papular Cutaneous Mastocytosis (MPCM) (e.g. Urticaria Pigmentosa) Isolated Mastocytoma Diffuse Cutaneous Mastocytosis (DCM)
Indolent Systemic Mastocytosis (ISM)	<i>Provisional variant</i> Bone marrow Mastocytosis (BMM)
Smouldering Systemic Mastocytosis (SSM)	
Aggressive Systemic Mastocytosis (ASM)	
Mast cell leukemia (MCL)	
Systemic Mastocytosis Associated to another Hematological Neoplasia (SM-AHN)	
Mast cell sarcoma (MCS)	

Drug allergy and mast cell diseases

The frequency of underlying clonal MC diseases (CMD), including mastocytosis and MMAS, in patients with drug hypersensitivity is still unknown. In fact, few studies have tried to investigate undetected CMD in this population.

Some recently published case reports have indicated an association between severe systemic reactions during general anesthesia and persistent raised tryptase serum levels, but BM biopsy was performed only in a few cases [20–22]. In addition, anaphylaxis to iodinate contrast media has been described in a patient who was subsequently diagnosed with SM [23] and a case of acetylsalicylic acid-dependent anaphylaxis to carrots was reported in a young patient with SM, in whom an oral allergy syndrome to raw carrots was confirmed by an oral provocation test [24].

As opposed to hymenoptera venom anaphylaxis in which it was previously shown that more than 85% of patients with raised tryptase values had CMD [7], the association between severe systemic reactions to drugs and CMD is far lower. Only selected studies have tried to investigate underlying CMD in patients with drug hypersensitivity reactions. One study evaluated the frequency of CMD in patients with food or drug-induced anaphylaxis: out of 86 patients with drug hypersensitivity, only seven (8.1%) had serum tryptase levels > 11.4 ng/ml [7] and, among these, only one out of five BM-tested was finally diagnosed with SM. Moreover, the authors observed that the severity of reactions was significantly greater in patients with drug hypersensitivity. These data were confirmed in another study evaluating the clinical, biological and molecular characteristics of patients with anaphylaxis and other symptoms leading to the suspicion for mastocytosis without skin involvement: the most common trigger for anaphylactic episodes in patients with CMD was hymenoptera sting, whereas drugs were mostly involved as a trigger in non-clonal MC

disorders [8]. In other studies on drug hypersensitivity, including serum tryptase measurements after reactions, BM biopsies were not performed [25, 26].

Although much less common than after hymenoptera stings, fatal anaphylaxis may occur after the intake of anesthetic drugs, NSAIDs, antibiotics and opioids. Therefore, from a practical point of view in the management of patients with mastocytosis, it is very important to know which drugs they can use and which ones they should avoid. Recently, members of the European Network for Drug Allergy (ENDA) published a position paper on this topic based on a critical review of the available literature regarding drug classes mainly involved in the development of immediate hypersensitivity reactions in patients with CMD [27••]. The authors, based on a literature's data review, tried to give some recommendations regarding the challenging management of drug in these patients.

Mast cell diseases and general anesthesia

General anesthesia is considered a risk procedure for patients with mastocytosis, but knowledge of their perioperative drug safety is still scarce and based on case reports and small case series. Patients with mastocytosis have indeed a higher risk to develop anaphylactic reaction during general anesthesia, because mediator release can be elicited by mechanical irritation of tissues, stress or administration of drugs.

During anesthesia the overall incidence of anaphylaxis (or anaphylactoid reactions) in the general population ranges from 0.004% to 0.03% [28, 29]. In a first study performed in patients with mastocytosis, the risk of anaphylaxis during general anesthesia reaches 0.6% [30]. A more recent retrospective study done in 501 patients with mastocytosis (459 adults and 42 children undergoing 726 anesthetic procedures) showed low frequency of moderate perioperative MC mediator release-associated symptoms both in adults and in children (4 and 2%, respectively); in addition, one child (2%) and three adults (0.3%) displayed anaphylaxis [31••].

General anesthesia is therefore considered a high risk procedure for patients with mastocytosis and then, in case of surgical intervention, especially for elective procedures, an adequate preparation of the patient must be organized by achieving some essential goals for drastically reducing the appearance of complications pre-, intra- and post-operative [32]. Previous episodes of intraoperative anaphylaxis increase the risk; therefore, medical history and anesthesiology records from previous surgeries should be obtained in all patients. Furthermore, a great role is assigned to physical triggers such as sudden temperature changes in patients and the operating room, infusion of cold solutions, wide tissue trauma, friction and other mechanical factors, and; therefore, they should all be avoided [33••]. Also, preoperative anxiety control plays a key role in the conduct of a safe anesthesia, and premedication with benzodiazepines must be considered in selected patients, as MC degranulation can be triggered by anxiety. Medications and equipment to treat perioperative anaphylaxis should be readily available [34••]. Any regular maintenance medication taken to maintain MC cell stability and limiting the effects of MC mediators should be continued during the operation.

Although no evidence clearly supports administration of premedication prior to anesthesia to prevent or reduce severity of reactions, there is also no evidence of the contrary, and premedication with H1/H2 anti-histamines, corticosteroids and montelukast should be considered, depending on the risk of the individual patient [33••].

Induction of general anesthesia, involving the simultaneous administration of several drugs, is one of the most stressful stages for the patient and more worrying for the anesthesiologist. Although it is often impossible to know in advance how a patient may respond to the administration of drugs, it is proved that mast cell activation in response to propofol, ketamine, or midazolam is rare [35, 36]. For the maintenance of general anesthesia, the recommended volatile anesthetic is sevoflurane; this, in fact, is an inhibitor of mast cell activation. It can also be used as a drug hypno-inductor especially in pediatric surgery [33••, 37].

The choice of the analgesic drug must be well assessed. Opioids such as fentanyl and remifentanyl (excluding morphine) seem safe enough for the management of intraoperative pain, but their administration should be carried out slowly because all opioids can easily cause a degranulation [34••, 35]. Medications such as those belonging to the class of NSAIDs conversely are to be avoided unless there is a previous history of intake by the patient.

Among the curares the safest for patients with mastocytosis is certainly cis-atracurium, few are the episodes of mediators release with the use of rocuronium; mivacurium instead is absolutely to be avoided for the high frequency of histamine release also in patients without mastocytosis.

In patients with mastocytosis regional anesthesia it is generally considered to be safe, since true allergic reactions caused by local anesthetics, are considered to be rare events [30, 33••]. In general, local anesthetics in the "esters" group should be avoided, (this group includes procaine, chlorprocaine, tetracaine, benzocaine). Anaphylactic reactions to local anesthetics of the "amide" group are much rarer and drugs such as lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine and ropivacaine can be used with some confidence in patients with mastocytosis. There are no reports of severe adverse reactions to local anesthesia performed before BM examination.

The intraoperative anaphylactic shock management is no different from the usual [33••]. During surgery, the patient with mastocytosis may experience sudden degranulation at any time of the procedure and management of complications in patients with mastocytosis must be conducted as for any other patient. This includes the administration of O₂ to 100%, anti H1 and anti H2, epinephrine if hemodynamic collapse, the Trendelenburg position, volume administration (crystalloids) and beta2 agonists in case of bronchospasm without hypotension.

Mast cell diseases and radio contrast media

In the literature there are a few reports on the concurrence of mastocytosis in patients with Radio Contrast Media (RCM) hypersensitivity reactions and on RCM hypersensitivity in patients with mastocytosis [16, 23, 38–40].

Based on data up to now available RCM appears not to be a common trigger of anaphylaxis in patients with mastocytosis. In a large multicenter study, which included 122 patients with immediate RCM hypersensitivity, where concurrent diseases were evaluated in the study protocol, but without obligatory baseline serum tryptase measurement and skin inspection, none of the patients had the diagnosis SM [41]. In an Italian study of 86 adult patients with severe drug hypersensitivity, RCM was responsible for anaphylaxis with loss of consciousness in one patient with a basal tryptase level of 20.1 ng/ml, but CMD was excluded by BM biopsy and analysis of the *c-kit* mutation D816V [42]. Furthermore, in three studies that analyzed the frequency of anaphylaxis in patients with mastocytosis taken together, RCM was the trigger in two of 321 adults (108 with anaphylaxis) and none of 93 children (seven with anaphylaxis) [14, 16, 18].

No specific recommendation for RCM was proposed to prevent anaphylaxis in patients with mastocytosis and previous drug anaphylaxis and its utility has to be established [16, 43]. Therefore, as RCM can induce severe, sometimes fatal, reactions in the general population (even non-ionic 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 [27••].

Mast cell diseases and non-steroidal anti-inflammatory drug (NSAIDs)

Acetylsalicylic acid has been implicated as a co-factor in augmenting anaphylaxis in patients with food associated exercise-dependent systemic anaphylaxis; [44, 45] and in a patient with SM with oral allergy syndrome to carrots, in whom flushing, dizziness and respiratory distress occurred only after prior exposure to acetylsalicylic acid 60 minutes before consumption of carrots, but not by ingestion of carrots alone [24]. In such cases, aspirin may act to increase gastrointestinal permeability, thereby enhancing systemic distribution of ingested allergens [44].

As with aspirin, there is a reluctance to prescribe NSAIDs to patients with SM. The possible reasons for this may be derived from literature reports of adverse reactions to this class of drugs in general. In a series of 212 Mastocytosis patients (116 adults, 96 children) 14% of adults but only 2% of children reacted to aspirin or other NSAIDs (pyrazolone, diclofenac, ibuprofen, naproxen). Symptoms consisted of anaphylaxis, followed by urticaria, asthma, flushing and angioedema [46].

However, when tryptase levels were assessed in 284 patients with a history of NSAID hypersensitivity only 9.2% were found to have a basal tryptase value of >10 ng/mL. Basal tryptase values >20 ng/mL were associated with severe anaphylaxis only in venom allergic subjects, but not in NSAID hypersensitive patients [47]. In these series of 284 patients, a diagnosis of ISM was possible in only three patients. Based on these findings and the fact that the severity of hypersensitivity reactions was not

increased in patients with elevated tryptase values, the current practice to avoid NSAIDs in SM may be unwarranted.

Mast cell diseases and other drugs

There are some reports of anaphylaxis triggered by antibiotics, especially beta-lactams (amoxicillin, ampicillin, penicillin V), or aminoglycosides [16, 18]. A case of anaphylaxis after penicillin skin testing in a woman with high levels of basal tryptase and suspected beta-lactam allergy was reported [48].

Limited data are available regarding the safety of drugs in children. In one study 133 children with various forms of CM were evaluated and reactions to medications were registered in 12 patients, most with the maculo-papular variant of CM. Six of these reactions were due to beta-lactam antibiotics and three to acetaminophen and two to vaccines [49•]. In another study the authors evaluated 111 children with CM in order to identify predictors for severe MC mediator release symptom. They showed that only four children had hypersensitivity reactions with drugs, three of them with a maculo-papular pattern, and the culprit drugs were dipyrone and diclofenac in one case, ibuprofen in two cases and polyvitaminic complex in one [50].

Conclusions

In patients who have never experienced adverse reactions to drugs, previously and continuously tolerated medications 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. 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, testing (e.g., skin testing, provocation test) under close supervision.

The anesthetic procedures must be managed as high-risk procedures in mastocytosis patients, since it is difficult to predict the presentation of MC mediator related symptoms. In this line, it is recommended to give prophylactic anti-mediator therapy based on H1/H2-antihistamines and/or benzodiazepines (adults) 1 hour before the anesthesia; as well as corticosteroids before general anesthesia or in symptomatic cases.

Compliance with Ethical Standards

Conflict of Interest

Patrizia Bonadonna, Roberta Zanutti, Alessandro Bisoffi Varani, and Mauro Pagani declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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