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Risk Factors and Management of Severe Life-Threatening Anaphylaxis in Patients with Clonal Mast Cell Disorders

Peter Valent
Department of Internal Medicine I, Division of Hematology & Hemostaseology, Medical University of Vienna, Austria and Ludwig Boltzmann Cluster Oncology, Medical University of Vienna, Austria

Abstract

Several different risk factors and conditions may predispose to severe life-threatening anaphylaxis. Systemic mastocytosis (SM) is one such condition. Although many SM patients are suffering from mild or even no mediator-related symptoms, others have recurrent episodes of severe anaphylaxis, with clear signs of a mast cell activation syndrome (MCAS) despite prophylactic therapy with anti-mediator-type drugs. In several of these patients, an IgE-dependent allergy is diagnosed. The severity and frequency of MCAS-reactions neither correlate with the burden of neoplastic mast cells nor with the levels of specific IgE or the basal tryptase level. However, there is a relationship between severe anaphylaxis in SM and the type of allergen. Notably, many of these patients suffer from hymenoptera venom allergy. Currently recommended therapies include the prophylactic use of anti-mediator-type drugs, long-term immunotherapy for hymenoptera venom allergic patients, and epinephrine self-injector treatment for emergency-situations. In patients who present with an excess burden of mast cells, such as smouldering SM, cytoreductive therapy with cladribine (2CdA) may reduce the frequency of severe events. For the future, additional treatment options, such as IgE-depletion or the use of tyrosine kinase inhibitors blocking IgE-dependent mediator secretion as well as KIT activation may be useful alternatives.

Keywords

Mast cells; IgE; Mast Cell Activation Syndrome; Tryptase

Introduction

Mastocytosis is a term that defines a rare group of disorders characterized by abnormal expansion and accumulation of tissue mast cells (MC) in one or more organ systems [1-6]. In many patients, typical skin involvement, usually in form of maculopapular lesions, is found. Cutaneous mastocytosis (CM) usually develops in childhood and has a very favorable prognosis. In many of these patients, cutaneous lesions resolve spontaneously during or after

Correspondence: Peter Valent, M.D., Department of Internal Medicine I, Division of Hematology & Hemostaseology and Ludwig Boltzmann Cluster Oncology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria, Phone + 43-1-40400-6085, Fax + 43-1-40400-4030, peter.valent@meduniwien.ac.at.

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puberty. Systemic mastocytosis (SM) is usually diagnosed in adulthood and is characterized by internal organ involvement, with multifocal compact infiltrates of MC [1-6]. In most cases, the bone marrow (BM) is affected [1-6]. Skin lesions are detectable in a majority of adult patients with SM. In most patients, the *KIT* mutation D816V is detected in clonal cells [7-11]. Neoplastic MC in these patients usually display cytomorphologic signs of atypia and express the LFA-2 antigen (CD2) and/or the IL-2 receptor alpha chain (CD25) [1-6,12-15]. In almost all patients fulfilling WHO criteria for SM, the basal serum tryptase level is persistently elevated (>20 ng/ml) [16-18]. The following subtypes of SM are listed in the current classification of the World Health Organization (WHO): indolent systemic mastocytosis (ISM), SM with an associated clonal hematologic non-MC-lineage disease (SM-AHNMD), aggressive SM (ASM), and MC leukemia (MCL) [19-23]. The smouldering variant of SM (SSM) was initially presented as a provisional subtype of ISM [19,20]. Later, however, SSM has been recognized as a separate category of SM [21,24]. Table 1 shows the current classification of mastocytosis as defined by the consensus group [3,19-23].

In all variants of SM, the release of several different proinflammatory and vasoactive mediators from MC may cause clinical problems [25-30]. Depending on comorbidities such as an allergic disease and other factors, the symptoms vary in severity, and range from mild flushing or headache to severe hypotension or even life-threatening anaphylaxis [25-30]. In severe cases, a MC activation syndrome (MCAS) is diagnosed [31-33]. The triggering factors often remain unknown. In other patients, a co-existing allergy is detectable [25-30] (Table 2). In many cases, therapy with anti-mediator-type drugs and MC-stabilizing drugs is sufficient to control symptoms [25-33]. In those with a documented allergy, immunotherapy (IT) may be considered and may be helpful in avoiding fatal hypotension-episodes [25-30]. For all patients, strict avoidance of triggering factors is essential [25-30]. However, in some of the patients, severe or even life-threatening events occur despite adequate anti-mediator-type drugs, IT, and prevention. For these patients, the optimal management remains a challenge.

The Frequency and Risk of Severe Anaphylaxis in Mastocytosis

About 10-20% of all patients with SM may experience at least one episode of severe life-threatening anaphylaxis during their lifetime [28]. In some of the patients with SM who suffer from severe episodes of anaphylaxis and thus from MCAS, a co-existing allergy, usually an IgE-dependent disease, is diagnosed [25-30]. The frequency and severity of such reactions differ from patient to patient, and little is known about the mechanisms and triggering factors underlying hyper-responsiveness of MC in allergic patients and in patients with SM. Only a few studies have investigated a potential relationship between severe symptoms and certain genetic patterns [34-36]. Other studies have shown a relationship between certain clinical and laboratory features and the risk of anaphylaxis [37-39]. In one study, elevated tryptase levels have been associated with an increased risk of severe mediator-related events [37]. By contrast, other studies have suggested that severe anaphylaxis occurs preferentially in patients with a low burden of neoplastic MC [38]. The only well-established risk factor for recurrent severe anaphylaxis may be an overt allergy against hymenoptera venom. In fact, several different studies have shown that venom

allergic patients with SM have a high risk for severe life-threatening anaphylaxis after bee or wasp stings [40-45].

Grading of Anaphylaxis in Mast Cell Disorders

Several different grading systems for anaphylaxis have been developed, such as the “Ring&Messmer Scale” [46] or the “Müller Scale” that can be used to grade symptoms in patients with insect venom allergy [47]. These scores may work in patients with mastocytosis suffering from anaphylaxis. In 2007, the consensus group has presented another scoring system, with the intention to optimize and standardize grading of symptoms in patients with MC disorders [21]. This grading system is useful for grading of mediator-related symptoms in all patients with SM and includes: grade 0 (no symptoms), grade 1 (mild, no therapy required), grade 2 (moderate, kept under control with anti-mediator therapy), grade 3 (not sufficiently controlled with therapy) and grade 4 (severe symptoms requiring hospitalization) [21]. The frequency of grade 4 events is also measured and included in the grading system: A (<1/year), B (>1/year and <1/month), and C (>1/month) [21]. Severe hypotension and MCAS may occur in any category of SM and even also in patients with CM without histologic evidence of systemic organ involvement. As mentioned, an allergen can be identified as specific trigger of anaphylaxis in a subset of cases [25-30]. The classification of “anaphylaxis” in mastocytosis is thus based on the presence (+) or absence (−) of IgE-dependent allergic reactions [21].

Mast Cell Activation Syndrome (MCAS)

MCAS can be diagnosed when a) recurrent systemic (usually severe) symptoms of MC activation (MCA) are found, b) involvement of MC can be documented, preferably by demonstrating an increase in the serum tryptase level during (or shortly after) an event, and c) the symptoms respond to therapy with anti-mediator-type or MC-stabilizing medication [31,32,48-52]. All three criteria must be met to diagnose MCAS [31,32,48,49]. The diagnostic (minimal) increase in serum tryptase is defined by the following consensus-formula: at least 20% of baseline level plus absolute 2 ng/ml [32]. Example: an increase from 10 (basal) to 16 ng/ml (measured during the event) is diagnostic because 10 + 2 (20%) + 2 = 14. It is important to collect a serum sample at the time of the event and to compare this value to a serum sample taken either before the event occurred or at least 2 days after complete resolution of all symptoms. In patients in whom the basal tryptase level is elevated, a search for an underlying MC disease has to be initiated [21,32,49].

In many cases, only 2 or even 1 of the criteria of MCAS can be documented because mediators were not measured (e.g. assay not available) or the patient did not respond to anti-mediator-type drugs. In other patients, no increase in the serum tryptase level can be demonstrated. In some of these patients, other MC-derived mediators such as plasma histamine, urinary histamine metabolites or prostaglandin D2 levels can be measured and may show an increase during anaphylactic episodes [53-56]. MC activation may also manifest as a less severe reaction so that MCAS criteria are not met, but the patients are still suffering from symptoms requiring therapy. In other words, not all anaphylactic (mediator-related, clinically relevant) symptoms can be classified as MCAS. Finally, basophil

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activation can also lead to severe symptoms mimicking MC activation (or even MCAS). As soon as MC activation is found, patients need to be examined for the presence of a clonal MC disorder [32]. In those in whom mastocytosis is diagnosed, the presence of clinically relevant MC activation (requiring therapy) should be indicated by the diagnostic label 'SY' (for SYmptoms) added as a subscript to the diagnosis (example: SM_{SY}) [21]. Again, however, not all patients with SM_{SY} are suffering from an overt MCAS [21,32].

Underlying Disorders and Classification of MCAS

Initially, the term MCAS was reserved for patients with severe MC mediator-related symptoms in whom criteria for an underlying MC disease or other condition were not fulfilled [31]. Later, this form of MCAS was defined as idiopathic MCAS [32]. In fact, MCAS usually develops on the basis of an underlying (systemic) disease, which can be an IgE-dependent disorder, another reactive condition, or a MC neoplasm [21,31-35,48-52] (Table 3). The MC neoplasm is usually classified as SM. However, MCAS may also occur in patients with CM. In patients with SM, neoplastic MC usually express the activating *KIT* mutation D816V, which is considered to play a role in the autonomous expansion and survival of neoplastic MC [6-10,57]. Moreover, KIT D816V has been implicated in the increased releasability of MC in SM, because KIT ligand-induced activation of normal MC leads to enhanced IgE-dependent mediator release [58-60]. However, in several patients with SM, no mediator-related symptoms can be recorded even if the burden of neoplastic MC is very high, which argues against a major role of KIT D816V in the hyper-responsiveness of MC.

Based on the underlying disease, MCAS can be classified and thus diagnosed as primary MCAS, secondary MCAS and idiopathic MCAS [31,32,49] (Table 3). In primary MCAS, *KIT*-mutated, clonal MC are found. The underlying disease in these cases may be CM or SM [31,32,49]. However, even in the absence of CM or SM, a primary MCAS can be diagnosed. In these patients, monoclonal MC are found but only one or two minor SM criteria are demonstrable, so that the diagnosis SM cannot be established [31,32,49] (Table 3). In such cases, the follow-up may reveal progression to an overt MC disease (usually SM). Most patients with secondary MCAS are suffering from an IgE-dependent allergy [31,32,49-52]. If neither an allergy or other reactive disease-process nor a monoclonal MC population (*KIT*-mutated) is found, the diagnosis 'idiopathic MCAS' is appropriate (Table 3).

Treatment Options and Response Evaluation

The most important therapeutic manoeuvre is to avoid any agents and situations that may provoke an allergic reaction [21,32]. Patients at risk are also advised to take prophylactic medication life-long and to carry 2 or more epinephrine-self-injectors for use in emergency situations according to prescribed instructions. Mild symptoms (grade 1) do not require any drug therapy and grade 2 symptoms can usually be kept under control with proper anti-mediator-type drugs. These mediator-targeting drugs are prescribed according to published algorithms [21,32] and the individual situation in each case. A summary of most commonly prescribed prophylactic anti-mediator-type drugs is shown in Table 4. In patients with IgE-dependent anaphylaxis, specific immunotherapy (IT) should be considered, with recognition

of potential side effects [61-63]. Cytoreductive agents are usually not prescribed for treatment of mediator-related events in SM. However, in SM_{SY}-patients (MCAS) with a huge burden of MC, like seen in patients with SSM or ASM, cytoreductive therapy should be considered. In fact, it has been described, that in SSM patients with MCAS, the frequency of recurrent life-threatening anaphylaxis-events decrease substantially after treatment with cladribine (2CdA) [64,65]. Aspirin has previously been considered for treatment of severe anaphylaxis in SM. However, the doses of aspirin required to suppress PGD_2 production in MC are quite high. In addition, aspirin may provoke adverse events such as gastrointestinal problems (like bleeding) and can even induce hypotension (Table 2). Therefore, aspirin should only be administered in select cases and with great caution in SM. Other drugs, including MC-stabilizing agents or glucocorticosteroids have also been suggested. A new emerging class of MC-targeting drugs are broadly acting tyrosine kinase inhibitors (TKI), such as imatinib, PKC412 (midostaurin), dasatinib or masitinib [66-74]. Some of these TKI, like PKC412, block KIT D816V activation and thus MC proliferation in patients with SM [69-71]. However, KIT D816V is resistant against most of the other TKI, including imatinib and masitinib. An interesting aspect is that PKC412 not only inhibits KIT-dependent MC proliferation but also IgE-dependent (allergen-induced) activation and mediator-secretion in MC [75]. Therefore, TKI like PKC412 are considered as emerging and promising agents for patients with advanced SM, SM_{SY} and MCAS. Another approach is to deplete specific IgE in patients with SM_{SY} or MCAS [76,77]. However, for all these agents, controlled clinical trials demonstrating efficacy and safety in SM_{SY} or MCAS are currently lacking.

Responses to anti-mediator type therapy are classified as complete response, CR (complete resolution of symptoms), major response, MR (>50% reduction in severity or/and significant decrease in frequency of events: B→A or C→B), partial response, PR (10-50% reduction in severity; no major decrease in frequency), and no response, NR (<10% reduction; no decrease in frequency) [32].

Concluding Remarks and Future Perspectives

Patients with clonal MC disorders, such as SM, are at relatively high risk for the development of severe life-threatening anaphylaxis (MCAS). During the past few years, substantial knowledge concerning the triggers and mechanisms underlying MC activation and thus MCAS in these patients has been accumulated. In addition, solid criteria for the diagnosis and classification of MCAS have been established. Finally, new targeted drugs suppressing MC activation and/or MC proliferation in SM have been developed and are currently tested in clinical trials. Other novel drugs are effective in depleting free (uncomplexed) specific IgE, mediator production or mediator effects. For the future, the application of such drugs in defined algorithms may lead to advanced personalized medicine in MC proliferative disorders and MCAS.

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Table 1

Classification of mastocytosis*

Cutaneous mastocytosis (CM)
- Maculopapular CM (MPCM) = urticaria pigmentosa (UP)
- Diffuse CM (DCM)
- Mastocytoma of skin
Systemic mastocytosis (SM)
- Indolent SM (ISM)
- Smouldering SM (SSM)*
- SM with associated clonal hematologic non-mast cell-lineage disease (SM-AHNMD)
- Aggressive SM (ASM)
- Mast cell leukemia (MCL)
Extracutaneous mastocytoma
Mast cell sarcoma

* The classification relates to the WHO classification of 2008. However, in contrast to the WHO classification, SSM is now recognized as a separate category of SM.

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Table 2

Factors that can provoke anaphylaxis in patients with mastocytosis

Factor*	Potential mechanism
Insect (hymenoptera) venom	IgE-dependent allergy
Microbes (bacteria, viruses, others)	allergic reaction or direct effects on mast cells
Food	food allergies
Pollen and other plant allergens	IgE-dependent allergy
Stress	nerve-mast cell interactions
Cold temperature	temperature effect on mast cells
Aspirin	idiosyncrasy, Syk activation
Other drugs	allergy direct effects on mast cells
Alcohol	direct effect on mast cells
Toxins	direct effects on mast cells

* Most of these factors can also provoke anaphylactic reactions in (allergic) patients in the absence of mastocytosis

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Table 3

Mast cell activation syndromes (MCAS): variants and features

Type of MCAS	Clinical and laboratory features
Primary MCAS	*KIT* D816V-mutated monoclonal mast cells found
	a) Established SM: criteria to diagnose SM are fulfilled*
	b) Established CM: criteria for CM are fulfilled but the criteria to diagnose SM are not fulfilled
	c) Neither CM nor SM can be diagnosed, but monoclonal mast cells are found (1 or 2 minor SM criteria found)
Secondary MCAS	An underlying allergic or atopic disease is found but no monoclonal mast cells are detectable (wt KIT)
Idiopathic MCAS	No underlying allergy or atopy and no monoclonal (*KIT*-mutated) mast cells are detectable

SM, systemic mastocytosis; CM, cutaneous mastocytosis.

*The diagnosis SM can be diagnosed when at least one major and one minor SM criterion or at least 3 minor SM criteria are fulfilled.

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Table 4

Prophylactic treatment of mediator-related symptoms in patients with mastocytosis

Recommended treatment	Specific indication
Histamine receptor type 1 blocker	all patients
Histamine receptor type 2 blocker	all patients
Glucocorticosteroids	high risk patients* anaphylactic reactions known to be unresponsive to histamine receptor blockers
Immunotherapy (IT)	hymenoptera venom allergy**
Cladribine (2CdA)	SM with high mast cell burden (SSM) and severe, recurrent life-threatening anaphylaxis

SM, systemic mastocytosis; SSM, smoldering SM; SM_{SY}, SM with severe mediator-related symptoms requiring therapy.

* Even in high risk patients, glucocorticosteroids should not be prescribed routinely and only with great caution and with recognition that long-term treatment is associated with the risk of severe osteopathy in SM.

** In patients with SM in whom a bee or wasp venom allergy is diagnosed, life-long IT is usually recommended.