

Severe Life-Threatening or Disabling Anaphylaxis in Patients with Systemic Mastocytosis: A Single-Center Experience

Friedrich Wimazal^a Philipp Geissler^b Patrik Shnawa^b Wolfgang R. Sperr^{b, c}
Peter Valent^{b, c}

^aDepartment of Obstetrics and Gynecology, ^bDivision of Hematology and Hemostaseology, Department of Internal Medicine I, Medical University of Vienna, and ^cLudwig Boltzmann Cluster Oncology, Vienna, Austria

Key Words

Mast cell disease • Anaphylaxis • Histamine • Cladribine

Abstract

Background: Mediator-related symptoms in patients with systemic mastocytosis (SM) range from mild episodic to severe life-threatening events. **Methods:** We examined a series of 137 consecutive patients with mastocytosis (63 females and 74 males) referred to our center between 1988 and 2010. Almost all patients received prophylactic histamine receptor (HR1 and HR2) antagonists. **Results:** Forty-two patients suffered from one or more mediator-related symptoms (hypotension, headache, flush, abdominal cramping, diarrhea) requiring therapy (SM_{SY}). Severe life-threatening events (grade IV) occurred in 17 patients (12%). In 4 of these 17 patients, a deteriorating clinical course was recorded. One patient died of an apallic syndrome 1.5 years after an hymenoptera sting and cerebral hypoxia. One patient was disabled for months after an insect sting and cerebral hypoxia. Two patients with smoldering SM (SSM) suffered from severe recurrent hypotension requiring hospitalization and repeated resuscitation. Symptoms in these SSM patients did not respond to any of the antimediator-type drugs applied. However, after therapy with cladribine (2CdA), a major durable response was

obtained in both cases. In patients with aggressive SM and mast cell leukemia (n = 6), life-threatening mediator-related events (grade IV) were not recorded. **Conclusions:** SM may be accompanied by life-threatening mediator-related symptoms. Most of these patients have indolent SM or SSM. In patients with SSM_{SY} with uncontrolled symptoms (grade IV), therapy with 2CdA should be considered.

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Introduction

Mastocytosis is a term used for a heterogeneous group of disorders characterized by abnormal accumulation of mast cells (MCs) in one or more organs with or without skin lesions [1–4]. Cutaneous mastocytosis usually develops in early childhood and has a favorable prognosis [1–4]. In many of these patients, the disease resolves spontaneously during or after puberty. Systemic mastocytosis (SM) develops at any age and is characterized by multifocal compact infiltrates of MCs in the bone marrow as well as other organ systems [1–5]. In most of these patients, the somatic *KIT* mutation D816V is detectable [6–9]. Neoplastic MCs in these patients usually display cytomorphological atypia and express CD2 and/or CD25 [10, 11].

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Correspondence to: Prof. Dr. Peter Valent
Department of Internal Medicine I, Division of Hematology and Hemostaseology
Medical University of Vienna and Ludwig Boltzmann Cluster Oncology
Währinger Gürtel 18–20, AT–1090 Vienna (Austria)
Tel. +43 1 40400 6085, E-Mail peter.valent@meduniwien.ac.at

Table 1. Patients' characteristics and frequency of mediator-related symptoms

Diagnosis	Patients n	Median age at diagnosis years (range)	Female to male ratio	Median basal total serum tryptase, ng/ml	Mediator-related symptoms (MCA) in mastocytosis _{SY} , n				
					grade I	grade II	grade III	grade IV	grades II + III + IV
MIS	12	32 (20–47)	1:1.4	7 (2–64)	0	0	0	1 (8)	1 (8)
CM	27	30 (6–76)	1:0.6	11 (3–25)	3 (11)	0	0	0	0
ISM	74	43 (22–81)	1:1.3	36 (6–938)	11 (15)	14 (19)	5 (7)	13 (18)	32 (43)
SSM	7	47 (34–53)	1:0.8	353 (153–1,090)	1 (14)	1 (14)	0	2 (29)	3 (43)
SM-AHNMD	11	53 (46–74)	1:2.7	140 (11–664)	1 (9)	2 (18)	1 (9%)	1 (9)	4 (36)
ASM	5	40 (21–72)	1:1.5	271 (54–1,617)	2 (40)	0	1 (20)	0	1 (20)
MCL	1	34	–	970	0	0	1 (100)	0	1 (100)
all	137	43 (6–81)	1:1.2	30 (2–1,617)	18 (13)	17 (12)	8 (6)	17 (12)	42 (31)

Figures in parentheses represent ranges or percentages, as appropriate. Grade IV symptoms are associated with life-threatening anaphylaxis. Grading was performed according to consensus criteria [17]. MIS = Mastocytosis in the skin; CM = cutaneous mastocytosis; SM-AHNMD = SM with an associated clonal hematologic non-MC lineage disease; ASM = aggressive SM; MCL = MC leukemia; MCA = MC activation with mediator-related symptoms requiring therapy, also defined as mastocytosis_{SY}.

In almost all patients with SM, the basal serum tryptase level is elevated to greater than 20 ng/ml [12–14]. The following categories of SM have been defined by the World Health Organization (WHO): indolent SM (ISM), smoldering SM (SSM), SM with an associated clonal hematologic non-MC lineage disease, aggressive SM and MC leukemia [15–18].

In all variants of SM, the release of MC-derived vasoactive mediators may cause clinical problems [19–25]. Symptoms vary in severity and range from mild flushing or headache to severe hypotension or even life-threatening anaphylaxis [17, 19–25]. The triggering factors often remain unknown. In other patients, a coexisting allergy is detectable [19–25]. In many cases, therapy with anti-mediator-type drugs or an MC stabilizer is sufficient to control symptoms [19–25]. In those patients with a documented allergy, immunotherapy (IT) may be considered and may be effective and helpful to avoid fatal events [24, 25]. In each case, strict avoidance of triggering factors is essential [17, 22]. However, in some patients, severe or even life-threatening events occur despite adequate anti-mediator-type therapy, IT and prevention [19–25]. For these patients, the optimal management remains unknown.

We report on a cohort of 137 consecutive patients with mastocytosis diagnosed in our center. In 17 of these patients, severe life-threatening anaphylaxis occurred. Severe recurrent events resulting in clinical deterioration were recorded in 4 patients. These 4 patients are described in detail in this article.

Patients and Methods

Patients

A total of 137 consecutive patients with mastocytosis (female to male ratio 1:1.2) were seen in our department between 1988 and 2010. The median age at diagnosis was 43 years (range 6–81 years). Diagnoses were established according to criteria provided by the WHO and by the US/EU Consensus Group [15–18]. Only 3 patients had childhood mastocytosis (ages: 6, 11 and 14 years). All other patients suffered from adult MC disease (ages: 16–81 years). Patients with mastocytosis and mediator-related symptoms requiring therapy, i.e. grade II, III or IV [17] (n = 42, 31%) were classified as having mastocytosis with MC activation. The patients' characteristics are shown in table 1.

Staging Investigations and Classification of Mastocytosis

A physical examination, including a detailed inspection of the skin and abdomen (liver and spleen size), was performed in all patients. In most adult patients, a bone marrow biopsy (with immunohistochemistry) and aspiration (for morphology, flow cytometry and *KIT* mutation status) were performed in order to establish the diagnosis of SM using diagnostic criteria [15–18]. The presence of the *KIT* D816V mutant was examined according to recommended techniques [17]. In patients who refused a bone marrow biopsy but presented with typical skin lesions, the diagnosis mastocytosis in the skin was established following published guidelines [17]. Further staging investigations included an ultrasound of the abdomen (liver and spleen size), a complete blood count, serum chemistry, immunoglobulins and a basal serum tryptase level, which was determined by a commercial fluoroenzyme immunoassay (Pharmacia Diagnostics, Uppsala, Sweden).

Evaluation and Grading of Mediator-Related Symptoms and Response Evaluation

The following symptoms were recorded: vascular instability (hypotension), headache, flush, abdominal cramping and diar-

rhea. Grading of mediator-related symptoms was performed according to published guidelines [17]. Patients were classified as having symptoms of grade 0 (no symptoms), grade I (mild infrequent symptoms requiring only prophylactic therapy), grade II (moderate symptoms, usually kept under control with antimediator drugs), grade III (severe recurrent symptoms despite daily intensive antimediation therapy) or grade IV (severe life-threatening anaphylaxis requiring emergency treatment and hospitalization) [17]. The frequency of grade IV episodes (grade A: less than 1 episode per year; grade B: 1–12 episodes per year; grade C: >12 episodes per year [17]) was also recorded. Severe anaphylaxis was defined as one or more events requiring resuscitation or intensive care and hospitalization to manage hypotension and shock (grade IV).

Responses to therapy were classified as described previously [17]: (1) complete regression (all symptoms completely resolved for at least 12 months; after 24 months: continuous complete regression); (2) major regression (improvement of symptoms by >50% and/or decrease in frequency of severe grade IV events from B to A or from C to B); (3) partial regression (improvement of symptoms by 10–50% and/or decrease in frequency of severe events by less than 50%), and (4) no regression (<10% improvement in symptoms and no decrease in frequency of severe events) [17].

Results

Description of Case Reports

In 4 of the 137 patients (3%), severe life-threatening anaphylaxis resulting in a severe handicap with or without transient or permanent disability occurred. These patients are described in detail below.

Patient 1

A 48-year-old female patient with known SM was referred because of severe recurrent anaphylaxis. Skin lesions were known to have occurred since 1971. The diagnosis of SM was established in 1998. Clinical and laboratory examinations and bone marrow studies revealed SSM (KIT D816V+) with slight anemia and a slight increase in spleen size. The serum tryptase level ranged between 819 and 1,090 ng/ml. Mediator-related events occurred at least every month and were characterized by severe hypotension and shock requiring emergency treatment, often with resuscitation and/or hospitalization with admission to the intensive care unit (SSM_{SY}, grade IVB). Symptoms occurred despite treatment with histamine receptor blockers, MC stabilizers and glucocorticosteroids. In 2003, therapy with cladribine (2CdA; 0.13 mg/kg i.v. per day, days 1–5 per cycle) was started. There was no known allergy. Between December 2003 and October 2004, the patient received 6 cycles of 2CdA. Later, in 2007, she received 3 additional cycles of 2CdA. Details

concerning therapy have been published elsewhere [26]. During treatment with 2CdA, mediator-related symptoms improved substantially. Notably, no further severe life-threatening events occurred after therapy with 2CdA, i.e. during the last 2 years of observation (until January 2011).

Patient 2

A 41-year-old female patient was diagnosed as having KIT D816V+ SSM in 1996. Her serum tryptase level was 175 ng/ml. There was no known allergy. During the following years, the patient had recurrent episodes of severe mediator-related symptoms with hypotension and anaphylaxis requiring hospitalization (SSM_{SY}). Symptoms occurred despite treatment with histamine receptor antagonists and glucocorticosteroids. In 2003, she received interferon- α (5 million units s.c. 3 times a week). During treatment with interferon- α , her symptoms did not improve. However, liver enzymes increased and interferon- α was discontinued. In February 2005, 2CdA therapy was initiated. She received 3 cycles of 2CdA. During 2CdA therapy, mediator-related symptoms improved substantially. However, she also developed a massive and long-lasting pustular skin exanthema requiring hospital admission and long-term treatment with antibiotics and glucocorticosteroids [26]. After 1.5 years, the exanthema resolved. Until January 2011, no further severe life-threatening anaphylactic events had occurred.

Patient 3

A 43-year-old male patient was referred because of a severe mediator-related event after a wasp sting. The presence of mastocytosis was already known and was confirmed by a skin biopsy. Because no bone marrow studies were performed, the diagnosis mastocytosis in the skin was established. The patient did not take prophylactic histamine receptor blockers. During a mountain tour, he collapsed after a wasp sting. Despite immediate resuscitation, prolonged cerebral hypoxia occurred and he developed an apallic syndrome. The basal serum tryptase level was 8 ng/ml. A radioallergosorbent test revealed wasp allergy (class II, normal serum IgE). Approximately 1.5 years later, he died from an infectious complication.

Patient 4

A 26-year-old male patient was diagnosed as having ISM in 1991. At that time he had a generalized maculopapular skin exanthema but did not suffer from mediator-related symptoms. The KIT mutation D816V was de-

tected in the bone marrow. The basal serum tryptase level was 71 ng/ml. He did not take continuous histamine receptor blocking agents. In August 2003, a yellow jacket sting led to fulminant hypotension and shock, with subsequent transient cerebral hypoxia despite immediate resuscitation and intensive care. As a consequence, the patient remained disabled and required a wheelchair for more than 6 months. Thereafter, his neurological situation improved slightly, and he slowly recovered. In 2004, specific IT (wasp allergy) was initiated. After 3 years, neurological symptoms had further improved. However, he never recovered completely and suffered from massive psychological problems despite continuous support during the next few years. Basal serum tryptase levels remained fairly stable (73 ng/ml in 2007). The patient is now on continuous histamine receptor blocker therapy and carries an epinephrine self-injector. No further severe mediator-related events occurred.

Therapy and Response to Therapy

Most patients received prophylactic or therapeutic histamine receptor (HR) antagonists (HR1 and HR2 blockers). In those with severe symptoms, 'MC stabilizers' (cromolyn sodium or ketotifen) or glucocorticosteroids were applied. All symptomatic patients were advised to carry an epinephrine self-injector. In the 2 patients with SSM and life-threatening anaphylaxis, cladribine was administered. After written informed consent was provided, patients received 9 cycles (patient 1) or 3 cycles (patient 2) of cladribine, each consisting of 0.13 mg/kg/day cladribine i.v. (2-hour infusion) on 5 consecutive days. Both patients received concomitant HR1 and HR2 antagonists as well as glucocorticosteroids during treatment with 2CdA. In both cases, therapy with 2CdA resulted in a marked decrease in basal serum tryptase levels (patient 1: pretreatment tryptase 949 ng/ml, posttreatment tryptase 137 ng/ml; patient 2: pretreatment tryptase 171 ng/ml, posttreatment tryptase 65 ng/ml) and a substantial decrease in the percentage of bone marrow MC infiltration as assessed by tryptase immunohistochemistry (patient 1: pretreatment 70%, posttreatment 45%; patient 2: pretreatment 25%, posttreatment 10%). In addition, a substantial improvement of mediator-related symptoms was recorded in both patients. In both cases, the response was classified as complete regression. In patient 1, a severe mediator-related event (hypotensive shock) was noted approximately 10 months after the first series (6 cycles) of 2CdA. Thereafter, she received another 3 cycles of 2CdA (between May and November 2007). In December 2008, she had another hypotensive event requiring hospitalization.

However, between December 2009 and January 2011, no further severe events occurred. In patient 4, specific IT (documented wasp allergy) was initiated after he had recovered from anaphylaxis and cerebral hypoxia.

Discussion

Mastocytosis is a heterogenous disease with regard to the clinical course. In a substantial number of patients, severe mediator-related symptoms occur [1–4]. Such symptoms can develop in any category of mastocytosis and can represent a serious or even life-threatening clinical problem [17, 19–25]. These symptoms may be confused with cardiovascular problems, allergic diseases, endocrinologic disorders or even psychiatric conditions [17, 27–29]. We report on 4 patients with SM in whom severe life-threatening and/or disabling anaphylactic events occurred. These patients were identified among a total of 137 patients with mastocytosis (including 98 with SM) seen in our referral center between 1988 and 2010. Prolonged hypotension following anaphylaxis and cerebral hypoxia were identified as major factors leading to a substantial handicap, clinical deterioration or even death in these patients. Our study also shows that 2CdA (cladribine) is not only effective in reducing the MC burden in SSM but may also be effective in counteracting MC activation, thereby lowering the risk of fatal anaphylactic events in these patients.

A number of previous and more recent studies suggest that mastocytosis patients have a highly variable clinical course, especially with regard to mediator-related symptoms [17, 19–29]. Whereas in some patients, absolutely no symptoms are recorded, others suffer from recurrent severe or even life-threatening events [19–25, 30–32]. Neither the severity nor the frequency of events appears to correlate with the category of mastocytosis or the burden of neoplastic MCs [20–28]. In our patients, life-threatening mediator-related events occurred in 4 out of 137 patients with mastocytosis. In many of the remaining patients, mediator-related events were also recorded but were less severe and, if recorded, did not lead to clinical deterioration or physical disability. Confirming the literature, we found no correlation between the severity of symptoms and the category of mastocytosis in our patients. However, in both patients in whom recurrent life-threatening anaphylaxis was recorded, the smoldering subtype of SM with a huge burden of MCs was diagnosed, whereas most patients in whom only one documented severe life-threatening event had occurred were found to

have low-grade SM with a low burden of MCs. Based on the clinical course in our patients, it is tempting to speculate that a high burden of MCs predisposes for recurrent severe life-threatening anaphylaxis, an assumption that was greatly supported by the fact that after successful cyto-reduction with 2CdA, a clear decrease in the severity and frequency of anaphylactic events was recorded in both SSM patients examined.

Little is known at present about the mechanisms underlying massive mediator release from MCs in patients with mastocytosis. One frequently discussed underlying factor is the KIT-activating mutation D816V, which is detectable in neoplastic MCs in a majority (>80%) of all patients with SM and sometimes also in childhood mastocytosis [6–9, 33]. Notably, this mutation is associated with autonomous activation of the receptor, and once it is expressed in neoplastic MCs, the mutant may critically contribute to enhanced releasability of MCs in SM [33]. However, clinically, several patients with SM bearing the KIT D816V mutation did not show any signs of MC activation and severe mediator release even if the burden of MCs was (very) high. Therefore, other additional factors and mechanisms may also have a great impact and may be responsible for severe mediator-related symptoms in these patients.

One of these additional underlying conditions may be a known, unknown or occult allergy. In fact, it has been described that various allergic diseases, especially allergies to hymenoptera venoms, can represent a causative factor (mechanism) in fatal anaphylaxis in patients with mastocytosis [17, 19–33]. For these patients, IT is often recommended (table 2). However, even when treated with prophylactic antimediator-type drugs and IT, severe reactions to bee or wasp stings may occur in the presence or absence of a documented allergy. Therefore, it is of great importance to advise all patients with mastocytosis to strictly avoid any potential triggering factors that can provoke a reaction. This is of importance in all patients with mastocytosis independent of the burden of (neoplastic) MCs. In fact, even in patients with a low MC burden who have no known allergy and are completely asymptomatic, severe reactions may occur. It may be difficult to explain to such patients why these triggers may be harmful and why they should take continuous prophylactic antimediator-type drugs and carry an epinephrine self-injector. In this regard, it is noteworthy that not all of our patients with a low MC burden and sudden (first-time) life-threatening anaphylaxis had taken prophylactic histamine receptor blockers, and most of them did not carry an epinephrine pen. However, wheth-

Table 2. Proposed treatment for patients with SM_{SY}

Proposed treatment	Indication
Histamine receptor (HR1/2) antagonists	all patients (basic therapy)
Cromolyn sodium	gastrointestinal symptoms unresponsive to HR2 blockers
Glucocorticosteroids	severe mediator-related symptoms unresponsive to HR1 blockers
Immunotherapy	known allergy (hymenoptera venom) and severe anaphylaxis
Cladribine (2CdA)	SSM with severe and recurrent life-threatening anaphylaxis
Epinephrine (self-)injector	life-threatening hypotension

All patients with symptoms start with a combination of HR1 and HR2 antagonists. If this is not effective, other drugs are administered (in addition to HR blockers) based on symptoms and the organ systems involved. Epinephrine is an emergency drug used in patients with severe hypotension (anaphylactic shock) regardless of a previous history of hypotension and regardless of the type of mastocytosis.

er anaphylaxis in these patients would have been less severe if they had taken antimediator-type drugs remains unknown.

A number of observations and studies have shown that 2CdA is effective in patients with advanced SM [26, 34–37]. Patients with SSM may be particularly sensitive to this drug [26, 34–38]. From our data, one may conclude that 2CdA could be a useful drug to counteract MC activation in SSM patients. However, in our opinion, 2CdA should only be used if a patient does not respond to conventional antimediator-type drugs and when symptoms are extremely severe and recurrent in SSM (table 2). In other words, 2CdA should indeed be considered in SSM patients but is not regarded as first-line therapy for SSM. Another question is whether 2CdA should also be considered in other categories of SM, e.g. in patients with ISM and severe life-threatening anaphylaxis who do not respond to conventional antimediator-type drugs. This question is currently under discussion, and there is no generally accepted standard or recommendation available at present. When safety is acceptable and clinical trials show beneficial effects, such treatment may also be considered a reasonable approach for patients with ISM and severe mediator-related symptoms caused by MC activation (ISM_{SY}).

In summary, our data show that life-threatening and even disabling anaphylaxis can occur in patients with SM. A primary cause of disability is cerebral hypoxia following an anaphylactic shock, which is frequently seen after bee or wasp stings in these patients. Patients with a high burden of MCs, especially those with SSM, may have the highest risk. Whereas conventional antimediator-type drugs are often ineffective in preventing severe reactions in these patients, 2CdA may work in reducing the MC burden in SSM, thereby lowering the risk of severe

anaphylactic reactions. In daily practice, the potential risk of anaphylaxis has to be weighed against potential side effects. In patients in whom venom allergy is diagnosed, IT is recommended.

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