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High prevalence of anaphylaxis in patients with systemic mastocytosis – a single-centre experience

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Summary

Background Systemic mastocytosis (SM) is a clonal mast cells disorder characterized by the proliferation, accumulation and activation of mast cells in extracutaneous tissues. The clinical picture is heterogeneous and may range from asymptomatic to potentially fatal anaphylactic reactions due to excessive mast cell mediator release.

Objective The aim of this study was to investigate the prevalence and trigger factors of anaphylactic reactions among adult SM patients. We also explored the clinical spectrum of mast cell mediator-related symptoms in patients with SM.

Methods This descriptive study was performed among 84 consecutive adult (≥ 18 years) patients those were diagnosed with SM according to WHO criteria. Sixty-six of the patients also underwent a comprehensive allergy work-up.

Results Sixty of 84 patients with SM (71%) had bone marrow mast cell aggregates and fulfilled the major criteria for SM and 76 patients (91%) had indolent disease. Simultaneous occurrence of cutaneous mastocytosis was observed in 59 patients (70%). Thirty-six patients (43%) had had at least one episode of an anaphylactic reaction. The clinical courses of the reactions were usually severe and patients often presented with syncope attacks (72%). Most patients reacted after hymenoptera venom stings (19/36; 53%). In 39% (14/36), a clear aetiology could not be determined. While males and females were equally frequent among the patients with SM, anaphylaxis patients showed a male predominance (61%). Anaphylactic reactions occurred more frequently in patients without cutaneous engagement. The rate of allergy sensitization was significantly higher in SM patients with anaphylaxis as compared with non-anaphylaxis SM patients, 70% vs. 23%, respectively ($P = 0.0002$).

Conclusions and Clinical Relevance Anaphylaxis is more prevalent in patients with SM, predominantly in patients with atopic SM. Hymenoptera venom-induced and idiopathic anaphylaxis were the most frequent elicitors. Our findings implicate that all mastocytosis patients with anaphylaxis should undergo detailed allergological assessment before considering treatment and preventive measures.

Keywords anaphylaxis, atopic disease, hymenoptera venom, IgE sensitization, mastocytosis, prevalence, tryptase

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Introduction

Anaphylaxis is one of the most alarming emergency conditions in medicine. It can be defined as an acute, suddenly occurring, severe systemic hypersensitivity reaction in at least two organ systems, including skin/mucosal tissue with either airway compromise or reduced blood pressure [1].

Several epidemiological studies have been previously performed to determine the prevalence and incidence of anaphylaxis in normal populations; the findings, however, are often inconsistent [2–5]. This is mainly

because of diverse study designs among different populations and differences in the definition of anaphylaxis. It is generally accepted that anaphylaxis is a relatively rare condition with a yearly incidence of 8–50 per 100 000 person-years [2–5]. The lifetime prevalence of anaphylaxis has been calculated to be approximately 0.05–2.0% [6].

Mastocytosis refers to a heterogeneous disorder characterized by excessive accumulation, proliferation and activation of abnormal mast cells in several organs, including the skin, bone marrow, liver, spleen, lymph nodes and gastrointestinal tract [7, 8]. The true incidence and prevalence of mastocytosis is unknown, but the existing evidence suggests that it is a rare condition. In cutaneous mastocytosis (CM), mast cell accumulation is by definition limited to the skin, whereas in systemic mastocytosis, at least one extracutaneous organ/tissue is involved, most often the bone marrow [9]. According to WHO criteria, patients with systemic mastocytosis (SM) can be further classified into four major subvariants: indolent SM (ISM); systemic mastocytosis with associated clonal haematological non-MC-lineage disease (AHNMD); aggressive systemic mastocytosis (ASM) and mast cell leukaemia (MCL) [10]. In adults, the vast majority of patients have indolent disease, in which the percentage of mast cells in the bone marrow is usually below 5% [11], and the rate of mast cell proliferation is very low [12]. Indolent SM appears to have a favourable prognosis without decreased life expectancy or organ damage; however, in aggressive variants of SM, the survival of patients can be limited, because the infiltration of pathological mast cells into organs and tissues can induce end-organ damage [13].

The clinical picture of systemic mastocytosis is extremely heterogeneous ranging from asymptomatic disease to a highly aggressive course with multisystem involvement. In patients with indolent disease, symptoms result from the local or remote effects of excess mediator release from mast cells, such as histamine, proteases, leukotrienes and prostaglandins. These, so-called mast cell mediator-related symptoms include flushing, pruritus, palpitations, dizziness, hypotension, syncope, breathing difficulties, abdominal pain, nausea, vomiting, diarrhoea, headache, sweating, lethargy, fatigue, lack of concentration, irritability, anxiety, depression, arthralgia and myalgia. Symptoms may either occur isolated or in some patients a constellation of symptoms may resemble an anaphylactic reaction, which might be life-threatening as in the appearance of anaphylactic shock [14].

The results of previous studies and clinical observations indicate a strong association between anaphylaxis and mastocytosis, and the prevalence of anaphylaxis has been reported to be 20–56% in adult patients with various forms of mastocytosis [15–17]. The aim of this observational study was to analyse clinical manifestations among patients with SM in a cohort of 84 consecutive adult patients, in particular symptoms related to mast cell activation, such as anaphylaxis. Further, we sought to determine the prevalence and common aetiological factors of anaphylaxis in these patients.

Methods

Patients

The Mastocytosis Centre at Karolinska University Hospital was established in 2006. Between January 2006 and December 2011, a total of 142 consecutive adult patients (≥ 18 years) were referred to the centre because of clinically suspected mastocytosis. All patients underwent medical evaluation including bone marrow investigation to determine potential underlying systemic mast cell disease.

Diagnosis of systemic mastocytosis was carried by a complete clinical and physical work-up together with routine laboratory chemistry and peripheral blood differential count. Mast cells in bone marrow biopsy samples were evaluated, following previously established methods and criteria for morphology [18], histology and immunohistochemistry [18, 19], flow cytometry [20] and mutational analysis [21]. Blood samples for assay of baseline serum tryptase (ThermoFisher, Uppsala, Sweden) were drawn either on the day of bone marrow biopsy or the nearest possible day, but never at the time of anaphylactic reactions. A diagnosis of SM was established in 84 adult patients, 42 male and 42 females, using current WHO criteria [8, 10]. Further investigations included computerized tomography of the thorax and abdomen and the measurement of bone density.

Study design

Patients with diagnoses of systemic mastocytosis were enrolled in this descriptive observational study. In five patients with urticaria pigmentosa (UP), we found no bone marrow involvement and hence they were excluded. The study used a cross-sectional approach, in which the medical records of the 84 patients with SM, laboratory test results, imaging results and pathological analyses of biopsy materials were reviewed and analysed. Furthermore, the patients were evaluated as regards whether or not they had had mast cell mediator-related symptoms and anaphylactic reactions (at least one episode). In this study, we particularly focused on patients with anaphylactic reactions.

The study was approved by Stockholm's Ethics Review Board (Dnr: 2011/1750/-31/3), and all 84

patients included were informed about the study and provided their written informed consent to participate.

Allergy work-up

Sixty-four of the 84 patients (76%) went through comprehensive evaluation including meticulous investigation of their medical histories, carried out by the allergist, and allergy tests. The possible effect of general triggers, such as cold, heat, friction, emotional stress, physical exercise, alcohol or histamine-containing food, was evaluated. The remaining 20 patients (of whom three patients with anaphylaxis) were carefully assessed through their medical records.

The presence of symptoms and signs related to mast cell mediator release including flushing, pruritus, urticaria/angioedema, palpitations, dizziness, hypotension, syncope, breathing difficulties, abdominal pain, nausea, diarrhoea, headache and anxiety was evaluated in all patients. Anaphylactic reactions were diagnosed in accordance with NIH clinical criteria, when either reduced blood pressure or associated symptoms such as syncope/pre-syncope and/or respiratory compromise or laryngeal oedema were present accompanied by the involvement of the skin–mucosal tissue or gastrointestinal symptoms [1]. In cases where assessments were difficult as a result of insufficient documentation, only patients who had syncope episodes after exposure to a likely or known trigger, with or without other accompanying symptoms, were assessed as having had an anaphylactic reaction.

Altogether, 59 SM patients underwent skin prick testing (SPT) with commercial extracts (ALK Allergologisk Laboratorium A/S, Horsholm, Denmark) of standard aeroallergens (birch pollen, grass pollen, mugwort pollen, cat/dog/horse danders, dust mites, moulds), food allergens (cow's milk, egg, peanut, hazelnut, wheat/rye/oat flour, fish, shrimp) and hymenoptera venom (wasp, bee). A positive (histamine dihydrochloride 10 mg/mL) and a negative control (NaCl 0.9%) were included. A skin test panel was considered valid if the histamine weal was at least 3 mm larger than the saline weal, and a skin test response was considered positive if the weal diameter was at least 3 mm larger than that elicited by the saline control [22]. In some cases, a specific IgE antibody test (Immuno CAP Phadiatop®; ThermoFisher) was also performed, often as a complementary tool, but also in five patients as the only allergy test. A specific IgE test was considered positive when values of > 0.35 kU/L were found. One or more positive reactions in SPT or specific IgE test against any tested allergens were considered as IgE sensitization. On the other hand, an atopic subject was defined as one with at least one positive reaction to SPT and/or CAP against aeroallergens. Atopic subjects who had a history of rhinitis or conjunctivitis (i.e. rhinorrhea, sneezing, congestion of the nose, red, itchy and water eyes), and/or had attacks of dyspnoea or wheezing when they came into contact with a particular allergen were considered as having an atopic disease. Subjects were fulfilled asthma diagnosis according to GINA criteria, that is, besides having typical clinical symptoms, had documented airway reversibility (> 12% and 200 mL improvement in FEV_1 from baseline 15 min after inhaled salbutamol), or had increased airway responsiveness to methacholine challenge (PD_{20} < 8 mg with FEV_1) [23].

Statistical evaluation

All analyses were performed using SPSS-20.0 for Windows software (SPSS Inc., Chicago, IL, USA). Categorical variables were analysed using the chi-square test or Fisher's exact test, when appropriate. Continuous variables are presented as median value and ranges. Values of $P < 0.05$ were considered statistically significant.

Results

Characteristics of patients with systemic mastocytosis

Patients with systemic mastocytosis were classified into different SM variants according to the international consensus and WHO criteria [7, 8]. Of 84 patients with SM, 76 were found to have indolent SM (including one with the smouldering systemic mastocytosis), six patients had SM-AHNMD and two patients were diagnosed with ASM subvariant. Concurrent occurrence of UP/CM was observed in 59 of the 84 patients (70%) in our study population. The patient characteristics are presented in Table 1.

The median age of patients in the study was 56 years (range 21–88 years), and we observed an equal distribution of males and females. Sixty of 84 (71%) patients with SM fulfilled the major criteria, whereas in the remaining 24 patients SM diagnosis was based on at least three minor criteria. Forty-three of 59 (73%) patients with SM with skin engagement fulfilled the major criteria. The *KIT* D816V mutation was analysed in 59 of the 84 diagnosed patients with SM and was detected in 53 of them (90%). Expression of aberrant phenotype markers CD2/CD25 on mast cells was investigated in all patients by immunohistochemical staining and also by flow cytometry analysis in 54 patients. Expressions of both aberrant markers were found in 74 of the 84 (88%) cases, whereas all 84 patients expressed aberrant marker CD25. Baseline serum tryptase levels were measured in 83 patients with SM and were found to be elevated (> 20 mg/L) in 73 of them (88%) with a median value of 52 ng/mL (range 4.3–710 ng/mL).

Table 1. Clinical characteristics of patients with systemic mastocytosis

	SM and SM variants				
Characteristics	SM (n = 84)	ISM n = 76 (91%)	SM-AHNMD n = 6 (7%)	ASM n = 2 (2%)	SM-CM n = 59 (70%)
Gender (M/F)	42/42	38/38	3/3	1/1	26/33
Presence of multifocal MC clusters	60/84 (71%)	54/76 (71%)	4/6 (67%)	2/2 (100%)	43/59 (73%)
Atypical MC morphology	81/84 (96%)	74/76 (97%)	5/6 (83%)	2/2 (100%)	57/59 (97%)
KIT mutation D816V, n (%)	53/59 (90%) 25 n/a	45/51 (88%)	6/6 (100%)	2/2 (100%)	42/44 (95%) 15 n/a
Levels of sBT					
> 20 ng/mL, n (%)	73/83 (88%) 1 n/a	66/76 (87%)	5/5 (100%) 1 n/a	2/2 (100%)	52/58 (90%) 1 n/a
11.4–20 ng/mL, n (%)	7/83 (8%)	7/76 (9%)	0	0	4/58 (7%)
Presence of mediator-related symptoms, n (%)	76/84 (90%)	69/76 (91%)	5/6 (83%)	2/2 (100%)	52/59 (88%)
Occurrence of anaphylaxis, n (%)	36/84 (43%)	35/76 (46%)	1/6 (17%)	0/2 (0%)	20/59 (34%)

SM, systemic mastocytosis; ISM, indolent systemic mastocytosis; SM-AHNMD, systemic mastocytosis associated with haematological non-mast cell lineage disease; ASM, aggressive systemic mastocytosis; SM-CM, systemic mastocytosis with cutaneous mastocytosis; MC, mast cell; sBT, serum baseline tryptase; n/a, not analysed.

Table 2. Distribution of allergen sensitization by SPT in 59 patients with systemic mastocytosis

	SM patients with anaphylaxis (n = 32)	SM patients without anaphylaxis (n = 27)	Total SPT (n = 59)
Positive	23	7	30
Pollens (birch, grass, mugwort)	16	4	20
Animal dander (cat, dog, horse)	13	1	14
Insects (bee, wasp)	12	2	14
Dust mites	3	1	4
Negative	9	20	29

SM, systemic mastocytosis; SPT, skin prick test.

Table 3. Distribution of atopic diseases in 64 patients with systemic mastocytosis who were investigated by SPT and/or CAP

	Overall prevalence (n = 64) (%)	SM patients with anaphylaxis (n = 33) (%)	SM patients without anaphylaxis (n = 31) (%)	P
IgE sensitization	30/64 (47)	23/33 (70)	7/31 (23)	0.0002
Atopy	19/64 (30)	14/33 (42)	5/31 (16)	0.029
Atopic diseases	14/64 (22)	11/33 (33)	3/31 (10)	0.033
Asthma	5 (8)	4 (12)	1 (3)	NA
Rhinoconjunctivitis	11 (17)	7 (21)	4 (13)	NA
Asthma and rhinoconjunctivitis	2 (3)	2 (6)	0	NA

SM, systemic mastocytosis; SPT, skin prick test; CAP, ImmunoCAP; NA, not analyzed.

The presence of any IgE sensitization was demonstrated in 30 of 64 investigated patients with SM (47%). Patients usually presented more than one sensitization. The most common allergens in SPT were found to be pollens 67% (20/30), followed by animal dander 47% (14/30), insects 47% (14/30) and dust mites 13% (4/30) as illustrated in Table 2. However, not all sensitized patients had clinical symptoms of allergy. Therefore, test results were carefully interpreted and allergens considered as aetiological factors only if they had any likely connection to the development of allergic reactions. When we considered sensitization with aeroallergens only after excluding single venom-sensitized patients, that is, atopy, we found an overall atopy rate of 30% (19/64). This was similar when it was compared with adult subjects in the general population in Sweden, 30% vs. 39%, respectively [24]. The presence of an atopic disease was determined in 18 of 64 investigated patients with SM (28%). Five patients (8%) were diagnosed with asthma, 11 (17%) rhinoconjunctivitis and two (3%) concomitantly asthma and rhinoconjunctivitis. However, in three patients with asthma and one patient with rhinitis, we were not able to show any IgE sensitization. The true prevalence was, therefore, 22% (14/64) after excluding these four patients. Results are shown in Table 3. The overall prevalence of asthma and rhinoconjunctivitis was not significantly different from the prevalence in the general Swedish population, which is estimated to be 8.3% for asthma and ranged from 17% to 26.9% for rhinoconjunctivitis [25, 26].

Clinical presentation

In our study population, the presence of mast cell mediator-related symptoms was observed in overall 76 of the 84 patients (90%). Symptoms in the gastrointestinal system such as abdominal cramps, nausea and diarrhoea were the most dominating, occurring in 53 of the patients (63%). These symptoms were followed by skin reactions such as flushing episodes and pruritus, and cardiovascular symptoms such as heart palpitations. Respiratory symptoms such as wheezing, dyspnoea and cough, or neuropsychiatric symptoms such as headache, anxiety and depression were observed in about a quarter of the patients. Figure 1 summarizes the distribution of different mast cell mediator-related symptoms.

Characteristics of patients with anaphylaxis

In this study, 36 of the 84 patients were identified as having had at least one episode of anaphylactic reactions (43%). In 22 of 36 patients, who were referred by allergist, anaphylactic episodes led to diagnosis of SM, whereas in the remaining 14 patients, the presence of anaphylactic reactions was assessed first after SM diagnosis. Of these 14 patients, 12 patients were referred by dermatologist due to UP/CM and the remaining two patients by haematologist. The patients had experienced a total of 77 anaphylactic episodes during an indefinite time period, that is, not only during the data collection time (2006–2011). While 22 patients had had single episodes, the remaining 14 patients accounted for 55 episodes. We did not observe any elicitor switch in patients during the investigation period. No biphasic anaphylactic episodes were reported. Table 4 summarizes the referral-based characteristic of anaphylactic episodes.

Anaphylactic reactions were often presented with cardiovascular symptoms. Hypotension and syncope were the most common reaction types in our study, where 26 of the 36 (72%) patients presented with attacks of unconsciousness. Unfortunately, blood pressure was not documented in all cases. These symptoms were followed by skin reactions and respiratory symptoms. Symptoms in the gastrointestinal system were not commonly presented. Figure 2 shows the modes of clinical presentation and a summary of the findings.

In our study, hymenoptera stings were found to be the most common elicitors of anaphylactic reactions, in 53% (19 of the 36 patients), all of which were caused by wasp stings. Hence, overall 23% of our patients with SM (19 of 84) were affected by hymenoptera-induced anaphylaxis. The venom sensitization was documented with SPT and/or specific s-IgE antibodies in 12 of 19 patients. In the remaining seven cases, despite convincing histories of venom-induced anaphylactic reactions, SPT and venom-specific IgE tests were negative. Therefore, diagnoses were made after careful considerations in these cases.

Reactions without known triggers, that is, idiopathic reactions, were also common in this cohort, 39% (14/36). In contrast, we observed only three patients with reactions after ingestion of food (against shellfish among others shrimp and IgE sensitization to shrimp was detected at low titres, 0.21 kE/L) or drugs (two cases). The culprit drug was a non-steroidal anti-inflammatory drug (NSAID) Diklofenac in both cases. In one case, there was a clear temporal association;

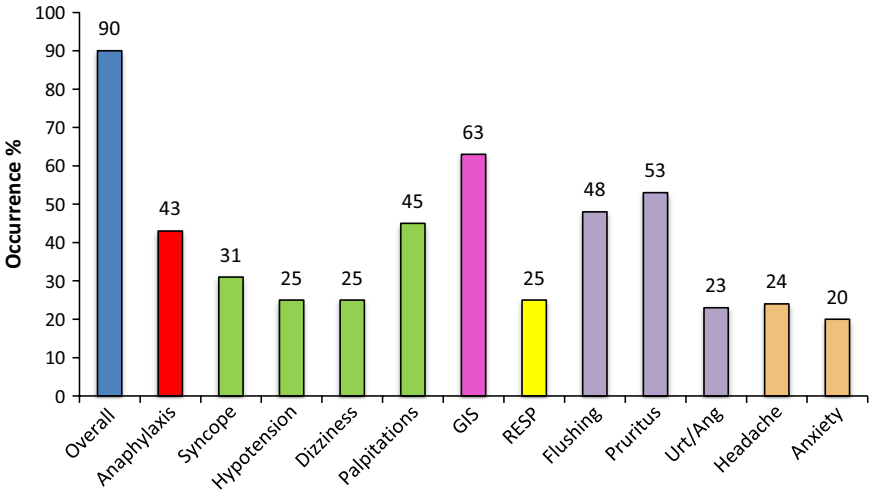

Fig. 1. Distribution of mast cell mediator-related symptoms in 84 patients with systemic mastocytosis. GIS, gastrointestinal symptoms such as nausea, abdominal cramps and diarrhoea; RESP, respiratory symptoms such as dyspnoea, wheeze-bronchospasm and stridor; Urt/Ang, urticaria and/or angioedema. Colors: ■, cardiovascular symptoms; ■, gastrointestinal symptoms; ■, respiratory symptoms; ■, skin symptoms; ■, neuropsyciatry symptoms.

Table 4. Referral-based distribution and the characteristic of anaphylactic episodes

Patients referred by	Number of episodes	Number of patients with single episodes	Number of patients with *wasp* as elicitor	HVA without proven sensitization
Allergists, $n = 22$	58	11	12	3
Dermatologists, $n = 12$	17	9	5	2
Haematologists, $n = 2$	2	2	2	2
Total, $n = 36$	77	22	19	7

HVA, hymenoptera venom anaphylaxis.

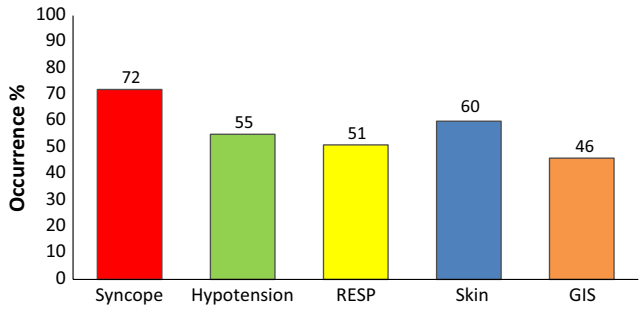

Fig. 2. Distribution of the most frequent clinical symptoms in 36 systemic mastocytosis patients with anaphylaxis. RESP, respiratory symptoms such as dyspnoea, wheeze-bronchospasm and stridor; Skin, involvement of skin/mucosal tissue such as flushing, pruritus, urticaria and swollen lips/tongue/larynx; GIS, gastrointestinal symptoms such as nausea, abdominal cramps and diarrhoea.

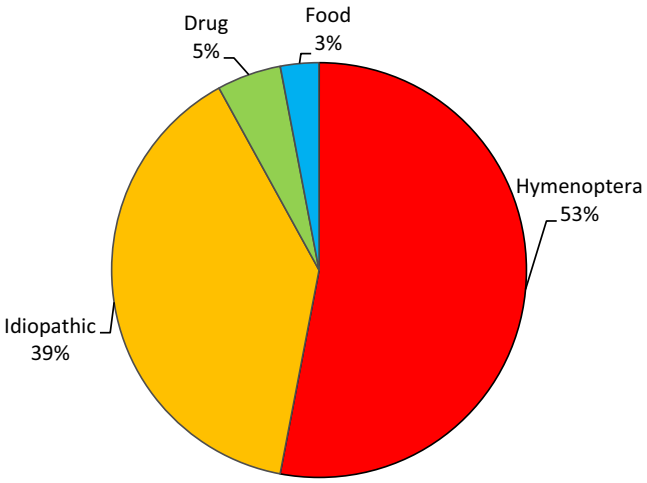

Fig. 3. Distribution of elicitors of anaphylactic reactions in 36 patients with systemic mastocytosis.

however, in the second case, NSAID was the most likely trigger. The distribution of different aetiological factors is summarized in Fig. 3. On the other hand, there was no substantial evidence to suggest that general triggers such as heat, cold, exercise, stress, histamine-containing food *per se* caused anaphylaxis.

Regarding IgE sensitizations, there was a significant difference when we categorized patients with SM into with or without anaphylaxis, because the prevalence of allergen sensitization was, as expected, higher in the anaphylaxis group, 23/33 (70%) vs. 7/31 (23%), respectively, $P = 0.0002$. Even when we only considered atopy rates, that is, taking into consideration reactions against only aeroallergens, differences between these two groups were still statistically significant, 14/33 (42%) vs. 5/31 (16%), respectively, $P < 0.03$. This was mainly due to the fact that 4 of 12 venom-sensitized patients and 8 of 14 patients with idiopathic anaphylaxis also had atopic sensitizations. The results were partly in accordance with the previous studies showing a higher sensitization rate in patients with idiopathic anaphylaxis (without mastocytosis) compared to the general population [27, 28]. Also, the presence of atopic diseases in overall differed between the two groups, 11/33 (33%) vs. 3/31 (10%), $P = 0.033$ (Table 3).

Moreover, the rate of anaphylaxis was significantly higher in patients with SM lacking skin involvement (urticaria pigmentosa), 16/36 (44%) vs. 9/48 (19%), $P < 0.02$. Regarding baseline tryptase levels, the difference between the groups was marginally significant as being slightly lower in the anaphylaxis group (median 37 ng/mL compared to 70 ng/mL, $P = 0.042$). Despite that female/male ratio was equal among all patients with SM, when only patients with anaphylaxis were analysed, the male predominance was obvious (61% male), although it did not reach statistical significance.

Discussion

In accordance with the earlier reports [16, 17], our findings showed a higher prevalence of anaphylactic reactions in patients with systemic mastocytosis, where 43% of the patients had had at least one episode of anaphylactic reactions. Two previous well-documented studies revealed the prevalence proportion of anaphylaxis in adults with the diagnoses of mastocytosis to be 22% (23% in indolent patients with SM alone) [16] and, quite similar to our finding, as high as 49% (56% in patients with SM alone) [17].

Discrepancies between different studies might be a result of heterogeneity of the patient cohorts, the definition of anaphylaxis (no universal agreement exists

yet) and varying recruitment strategies. In some studies, mastocytosis and systemic mastocytosis diagnoses have not been differentiated, because not all patients have been investigated by bone marrow biopsy. Another possible reason could be non-standardized SM investigation routines in different centres. For instance, allergy work-up is not routinely performed in all centres. Our patients were almost equally recruited via allergology, haematology and dermatology referrals, and all patients underwent BM biopsy before receiving a diagnosis of SM. Those with a diagnosis of CM alone were excluded from the study.

The main elicitors of anaphylactic reactions in our study were hymenoptera stings, and the triggering insects were exclusively wasp stings. These reactions accounted for 53% of the reactions. Despite a clear temporal association in all cases, however, we could confirm actual venom sensitization in only 12 patients (63%) by SPT and/or ImunoCAP. Interestingly, some reports describe negative venom skin test responses in up to 30% of patients with a convincing history [29, 30], and it is, therefore, generally accepted that not all venom-induced anaphylaxis in patients with SM could be confirmed with allergy tests because reactions may also occur by a non-IgE-mediated mechanism [31]. These negative reactions could also reflect a loss of sensitivity [29], as in four of our study subjects who experienced sting reactions decades earlier. Nevertheless, in remaining three patients, we could have probably confirmed venom sensitization by performing intracutaneous test or basophil activation test. Unfortunately, none of these patients were willing to undergo further investigations.

Other elicitors such as drugs and food seem not to be a major cause in this study, because only three patients showed likely reactions with these triggers. Although they are reported frequently in the literature, reactions with these elicitors often remain patient-reported, because it is difficult to verify as a result of insufficient data, lack of reliable *in vitro* tests and lack of provocation tests. Our results are consistent with those in another study that also demonstrated a weak association between food- and drug-induced anaphylaxis and mastocytosis [32]. Patients with unexplained triggers despite an extensive search, that is, those with idiopathic anaphylaxis, were the second most common group. Another interesting point to note was to observe that there were no elicitor switches in individual subjects because all patients maintained their elicitor profiles in consequent reactions by the time of study. In addition, evaluation of general triggers such as heat, cold, friction, stress and ingestion of histamine-containing food demonstrated that these triggers were only associated with the isolated organs, for example aggravation of the skin reactions, but never caused a systemic reaction themselves.

Our study confirms the feasibility and safety of the SPT in patients with SM, because none of the tested patients showed any kind of adverse reactions. The findings are in line with the results of another study [16]. The overall prevalence of IgE-mediated allergen sensitization and also atopy in SM patients does not differ from the prevalence in the general population in Sweden. This is in accordance with the earlier observations [16, 33]. Moreover, we also investigated the presence of atopic diseases in patients with SM and found that the prevalence (22%) in overall SM patients was comparable to previous studies that observed a prevalence of atopic diseases in 21% of patients with urticaria pigmentosa [33] and 28% in patients with mastoctosis [17]. Interestingly, when we compared SM patients with or without anaphylactic reactions, we found that the presence of atopy and atopic diseases in SM was associated with a higher prevalence of anaphylaxis.

It is noteworthy that we observed a clear male predominance among anaphylaxis patients, although this did not reach statistical significance. Interestingly, the male predominance was obvious even in different elicitor profiles, such as patients with hymenoptera-induced anaphylaxis or unexplained anaphylaxis. In agreement with the previous reports [16, 17], a particular reaction pattern with syncope and hypotension in regard to the clinical manifestations was observed in most of the cases, and the development of anaphylactic reactions was more common in patients without cutaneous engagement.

There seems to be a complex relationship between baseline tryptase levels, mast cell burden and the presence/absence of anaphylactic reactions in patients with SM. Although our study determined statistically significant differences between the groups as being slightly lower in the anaphylaxis group, in contrast to that however, a previous study [17] demonstrated higher serum tryptase values in those with anaphylaxis and thereby speculated that higher mast cell burden may potentially lead to spontaneous mast cell degranulation causing anaphylactic reactions. Recently, however, two comprehensive studies have challenged this phenomenon [34, 35] to define a distinct disease phenotype in SM patients with venom-induced anaphylaxis. Interestingly, there seemed not to be a correlation between mast cell burden and the presence/absence of anaphylaxis, because in most cases bone marrow mast cell numbers were quite low. Therefore, anaphylaxis in these patients could mainly be related to pathological alterations in mast cell activation processes rather than mast cell numbers *per se*. Nevertheless, this issue still remains to be proven, that is, whether these observations are only limited to SM patients with venom-induced anaphylaxis or if they also can be applied to overall anaphylaxis patients with SM.

The primary strength of this study arises from the fact that we were able to provide a complete and detailed description of patients with systemic mastocytosis in our centre. Moreover, we measured a reliable estimate of the point prevalence of anaphylaxis in our study population. However, our cross-sectional approach was a limitation, and therefore, a direct causality between systemic mastocytosis and anaphylaxis could not be established. In addition, the temporal relationship between SM and the presence/absence of anaphylaxis could not be assessed. Furthermore, we were dependent on complete and accurate recording of relevant information in the medical records as a result of lack of an allergy work-up in 20 cases in the study.

In conclusion, the present study has shown that the presence of mast cell mediator-related symptoms, in particular anaphylactic reactions, is clearly more prevalent in patients with systemic mastocytosis. Therefore, treatment and preventive measures in all systemic mastocytosis patients need to be tailored to the individual's symptoms after a complete allergological assessment. At present, there is no consensus of opinion on whether or not all patients with SM should be equipped with pre-loaded adrenaline injectors for self-treatment, because some patients with SM would most probably never experience an anaphylactic reaction. However, all anaphylaxis-prone patients must be equipped with adrenaline injectors after careful self-training. Patients with frequent episodes of anaphylactic reactions can be considered for omalizumab treatment [36, 37]. Moreover, all IgE-sensitized hymoneptera venom-induced anaphylaxis patients should be given lifelong venom-specific immunotherapy.

The above findings imply a *de facto* association between anaphylaxis and mastocytosis. What seems likely through our own clinical observations is that there should be an SM–anaphylaxis phenotype, at the moment without known phenotype markers. However, this notion still remains to be proven by prospective, preferably multicentre studies.

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Conflict of interest

The authors declare no conflict of interest.

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