

Indolent Systemic Mastocytosis with Elevated Serum Tryptase, Absence of Skin Lesions, and Recurrent Severe Anaphylactoid Episodes

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Key Words

Mastocytosis, classification · Tryptase · Anaphylaxis · CD25 · *c-kit* mutation

Abstract

Background: In contrast to aggressive mastocytosis, patients with indolent systemic mastocytosis (ISM) usually present with urticaria pigmentosa-like skin lesions. In those who lack skin lesions, mastocytosis is often overlooked or confused with endocrinologic, allergic, or other internal disorders. **Case Report and Results:** We report on a 33-year-old male patient in whom severe hypotensive episodes occurred after contact with ants or yellow jackets. Since no specific IgE was detected, the serum tryptase concentration was measured and found to be clearly elevated (70 ng/ml). Consecutive staging and examination of the bone marrow revealed ISM. The patient was advised to circumvent insect contact, to take antihistamines on demand, and to carry an epinephrine self-injector for emergency events. In a retrospective analysis of 40 patients seen between 1988 and 2003, only 2 had a life-threatening mediator-related episode before ISM was diagnosed. **Conclusions:** Our report confirms the diagnostic value of tryptase in patients with sus-

pected mastocytosis. In addition, the report suggests that the lack of typical skin lesions does not exclude an indolent form of mastocytosis even if the serum tryptase is clearly elevated. Finally, our case further shows that mastocytosis can be an important differential diagnosis to be considered in patients with unexplained anaphylactoid or other mediator-related symptoms.

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Introduction

The term mastocytosis denotes a heterogeneous group of disorders characterized by abnormal accumulation of mast cells (MCs) in one or more organ systems [1–4]. Cutaneous mastocytosis (CM) frequently develops in infancy and has a favorable prognosis [5]. In many of these patients, the disease resolves spontaneously during the second decade of life. Systemic mastocytosis (SM) can develop at any age and is characterized by multifocal infiltrates of MCs in one or more extracutaneous organs with or without skin involvement [1–4, 6, 7]. In the vast majority of these patients, the bone marrow is affected. A generally accepted hypothesis is that SM is a persistent clonal disease of myelomastocytic progenitors [1–4]. In most

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cases, the somatic *c-kit* mutation 2468A→T (D816V) is detectable [8–11]. Other criteria of SM include the histologic aspects of MCs (MC infiltrates = major criterion), cytomorphological (minor) criteria (spindle-shaped MCs), an increased serum tryptase level (>20 µg/ml), and expression of CD2 and/or CD25 in bone marrow MCs [12–18].

Based on the organ system(s) involved, clinical course, and the presence or absence of hematologic abnormalities (or a hematologic disease), SM can be subclassified. The WHO classification defines the following subvariants of SM: indolent SM (ISM), SM with an associated clonal hematologic non-MC cell lineage disease, aggressive SM (ASM), and MC leukemia (MCL) [19, 20].

A well-recognized clinical paradox is that patients with ASM or MCL often lack skin infiltrates [19, 20]. However, not all SM patients in whom skin lesions are absent, have aggressive disease. Likewise, patients may have isolated bone marrow mastocytosis, a special disease-variant characterized by the absence of skin lesions and a low serum tryptase level in most cases [19, 21]. By contrast, in most patients with ASM or MCL, serum tryptase levels are clearly elevated or very high [19, 21]. Therefore, a clearly elevated serum tryptase concentration has been considered as a potential indicator of aggressive disease in those SM patients who lack skin lesions [21].

In any category of mastocytosis, clinical problems may occur from massive release of MC-derived vasoactive mediators [22–28]. The triggering factors often remain unknown. In other patients, a coexisting allergy is found. Whatever the pathogenic basis of mediator release is, the occurrence of the respective symptoms has to be recognized as an important clinical sign to be addressed in these patients. Notably, in several cases fatal anaphylactoid reactions to insect stings, allergens, or other triggering factors have been reported [23–28].

We report on a patient in whom mastocytosis was detected after severe anaphylactoid reactions to ants and yellow jacket stings had developed. This patient did not show any skin lesions but exhibited a clearly elevated serum tryptase level.

Case Report and Methods

A 33-year-old male patient was admitted to our department in January 2004 because of episodes of anaphylactoid reactions after contact with insects (ants, yellow jackets) and an elevated serum tryptase level. The symptoms had been known for several years, and had increased in severity during the past 2 years. In 2002 and 2003, the patient had severe anaphylactoid episodes after ant bites and after a

yellow jacket sting. An allergy screen test, i.e. RAST (Pharmacia CAP FEIA, Pharmacia, Uppsala, Sweden) for honey bee, European hornet, and yellow jacket, was negative (<0.35 kUA/l). In addition, the serum IgE level determined by CAP IgE FEIA (Pharmacia) was normal (15.7, normal range <100 kU/l). However, serum tryptase appeared to be elevated, and the patient was referred to our hospital. At that time (January 2004), he was in good health without signs of mediator-related symptoms. There were no urticaria pigmentosa-like skin lesions and no organomegaly. Most of the laboratory parameters including blood count, serum chemistry, and coagulation tests were normal. Blood counts were as follows: white blood cell count 4,900/µl, hemoglobin 14.4 g/dl, and platelets 212,000/µl. The differential count showed 53% neutrophils, 2% eosinophil granulocytes, 5% monocytes, and 40% lymphocytes. The serum tryptase level amounted to 67 (normal range 1–15) ng/ml. Consecutively, a diagnostic examination of the bone marrow was performed.

Bone Marrow Histology and Immunohistochemistry

Bone marrow was obtained from the iliac crest after informed consent had been given. Specimens were fixed in ethanol-formaldehyde solution, followed by overnight decalcification in EDTA and embedding in paraffin. Immunohistochemistry was performed on 2-µm sections using the avidin-biotin immunoperoxidase staining technique as described [13, 29, 30]. Endogenous peroxidase was blocked by methanol and H₂O₂. Antibodies were diluted in Tris-buffered saline (TBS, pH 7.5) containing 1% bovine serum albumin, and applied at room temperature. The antibodies used and the staining technique are depicted in table 1. After each step, the tissue was rinsed twice in TBS. After incubation with antibodies, slides were washed and incubated with biotinylated horse anti-mouse or goat anti-rabbit IgG for 30 min. Sections were then washed and exposed to avidin and biotinylated peroxidase complex for 30 min. AEC was used as chromogen. Slides were counterstained in Mayer's hemalaun.

Flow Cytometric Investigation of Bone Marrow MCs

Bone marrow MCs were analyzed for expression of disease-related cell surface antigens by multicolor flow cytometry as described previously [18, 30, 31]. In brief, heparinized bone marrow samples were incubated with combinations of monoclonal antibodies (mAbs; table 2) and then subjected to erythrocyte lysis and fixation by exposure to FACS-lysing solution (Becton Dickinson, San Jose, Calif., USA). The FITC-labeled mAbs RPA-2.10 (CD2), MØP9 (CD14), MMA (CD15), 2A3 (CD25), and 581 (CD34), the PerCP-labeled mAb 2D1 (CD45), and the PE-labeled mAbs RPA-2.10 (CD2) and 515 (CD44) were purchased from Becton Dickinson. The PE-conjugated mAb 97A6 (CD203c) and the APC-labeled mAb 104D2D1 (CD117) were from Beckman Coulter/Immunotech (Marseilles, France). After immunostaining, cells were analyzed on a FACSCalibur (Becton Dickinson).

Analysis of c-kit Mutation D816V

Bone marrow mononuclear cells were isolated by Ficoll separation and subjected to RNA isolation using RNeasy as described [11]. mRNA was analyzed for the presence of the *c-kit* mutation 2468A→T (D816V) by reverse transcriptase (RT) PCR and restriction fragment length polymorphism (RFLP) analysis using *HinfI* digestion according to a published technique [11]. The human MCL cell line HMC-1 known to display the *c-kit* mutation D816V [32], served as a positive control.

Table 1. Specification of antibodies used for immunohistochemistry

Antibody	CD	Reactive antigen	Ig-type	Antibody dilution	Retrieval technique	Antibody source	Company
72F6	CD9	p24	IgG1	1:100	MW	m	NC
4C9	CD25	IL-2R α	IgG2b	1:50	MW	m	NC
QBEND10	CD34	HPCA-1	IgG1	1:50	MW	m	IT
Anti-kit	CD117	kit/SCFR	polyclonal	1:500	MW	r	D
G3	n.c.	Tryptase	IgG1	1:5,000	–	m	C
Anti-HDC	n.c.	HDC	polyclonal	1:500	MW	r	PG

IL-2R α = Interleukin-2 receptor α ; HPCA-1 = hematopoietic progenitor cell antigen-1; SCFR = stem cell factor receptor; HDC = histidine decarboxylase; MW = microwave oven pretreatment; m = mouse; r = rabbit; n.c. = not yet clustered. NC = Novocastra, Newcastle, UK; IT = Immunotech, Marseille, France; D = Dako, Glostrup, Denmark; C = Chemicon, Temecula, Calif., USA; PG = Progen, Heidelberg, Germany.

Table 2. Antibody combinations applied in multicolor flow cytometry

Tube No.	Monoclonal antibodies in tube				
1	CD34 FITC	mIgG1 PE	CD45-PerCP	CD117 APC	
2	CD34 FITC	CD203c PE	CD45-PerCP	CD117 APC	
3	CD34 FITC	CD2 PE	CD45-PerCP	CD117 APC	
4	CD34 FITC	mIgG2a PE	CD45-PerCP	CD117 APC	
5	CD34 FITC	CD44 PE	CD45-PerCP	CD117 APC	
6	CD34 FITC	PAR-2 PE	CD45-PerCP	CD117 APC	
7	mIgG1 FITC	CD34 PE	CD45-PerCP	CD117 APC	
8	CD2 FITC	CD34 PE	CD45-PerCP	CD117 APC	
9	CD25 FITC	CD34 PE	CD45-PerCP	CD117 APC	
10	CD63 FITC	CD34 PE	CD45-PerCP	CD117 APC	
11	CD14 FITC	CD34 PE	CD45-PerCP	CD117 APC	
12	CD15 FITC	CD34 PE	CD45-PerCP	CD117 APC	

Analysis of Serum Tryptase Concentrations

Serum tryptase levels were determined by a commercial fluoroenzyme immuno-assay (FEIA) purchased from Pharmacia Diagnostics (Uppsala, Sweden). The detection limit of the test amounted to approximately 1 ng/ml. Serum tryptase was measured in the patient presented, as well as retrospectively in a cohort of patients with SM referred to our department between 1988 and 2003.

Retrospective Analysis of Anaphylactoid Reactions in Patients with SM

A total of 40 patients with SM referred to our department between 1988 and 2003 were retrospectively examined for the occurrence of severe anaphylactoid reactions, the frequency of severe episodes (grade I = <1 episode/year; grade II = 1–3 episodes/year; grade III = >3 episodes/year), and the first time of occurrence of these symptoms in relation to the time of SM diagnosis. Severe episodes were defined as anaphylactoid events requiring resuscitation or intensive care and hospitalization to manage hypotension and shock.

Results

Bone Marrow Findings: Establishment of SM Diagnosis

Bone marrow histology showed typical multifocal dense (compact) infiltrates of MCs in Giemsa and chloroacetate esterase stains. Tryptase immunohistochemistry confirmed the presence of MC infiltrates (estimated grade of infiltration 5%). Within these infiltrates (major SM criterion), most MCs showed prominent (diagnostic) spindling (minor SM criterion) thereby confirming the diagnosis of SM (fig. 1A). As assessed by immunohistochemistry and multicolor flow cytometry, bone marrow MCs were found to express CD2 and CD25 as additional minor criterion (fig. 1, 2). In addition, MCs were found to react with mAbs against CD9, CD44, CD45, and CD203c (table 3). In contrast, MCs did not express CD14, CD15, or CD34. RT-PCR and RFLP results from analysis of

Table 3. Immunophenotype of neoplastic mast cells

Antigen	Expression in/on neoplastic mast cells		Phenotype of normal mast cells	
	IHC	flow	IHC	flow
CD2	n.t.	+	–	–
CD9	+	n.t.	+	+
CD14	n.t.	–	–	–
CD15	n.t.	–	–	–
CD25	+	+	–	–
CD34	–	–	–	–
CD44	n.t.	+	+	+
CD45	n.t.	+	+	+
CD117	+	+	+	+
CD203c	n.t.	+	n.t.	±

IHC = Immunohistochemistry; flow = flow cytometry; n.t. = not tested.

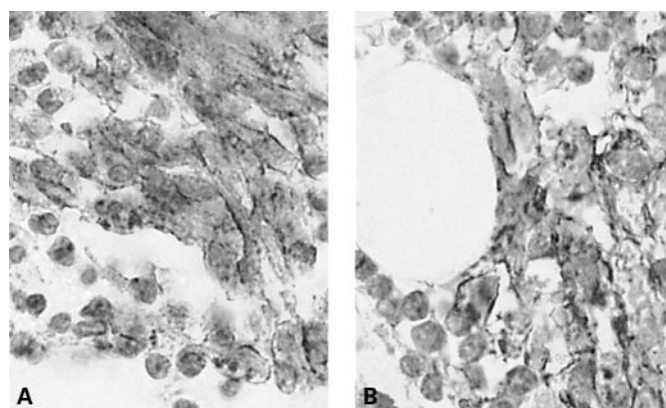
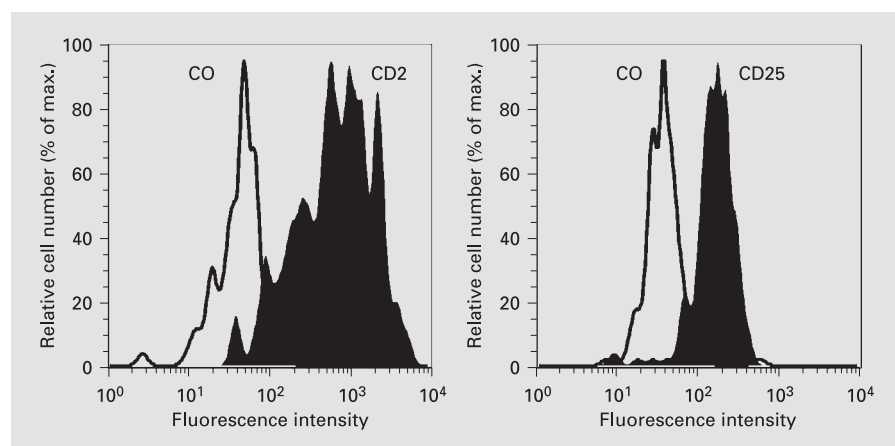


Fig. 1. Diagnostic bone marrow mast cell infiltrate detected by immunohistochemistry. Adjacent bone marrow sections were stained with an antibody against CD25 (**A**) and an antibody against CD9 (**B**). As visible, the focal dense mast cell infiltrate was composed of mostly spindle-shaped CD25+ and CD9+ mast cells without alteration of the surrounding bone marrow architecture.

Fig. 2. Detection of CD2 and CD25 on bone marrow mast cells. Multicolor flow cytometry analysis of bone marrow mast cells using an APC-labeled CD117 antibody for mast cell detection, a PE-labeled CD2 antibody, and a FITC-conjugated antibody against CD25. As visible, bone marrow mast cells expressed substantial amounts of both CD2 and CD25.



bone marrow cells revealed the presence of the *c-kit* mutation D816V. Based on bone marrow results, the diagnosis of SM was established.

Staging Investigations: Classification of Mastocytosis

To define the subtype of SM, staging investigations including a thorough and repeated investigation of the skin, were performed. Physical examination disclosed normal results without skin lesions. No hepatosplenomegaly or lymphadenopathy was found. X-rays of the chest and bones as well as ultrasound examination of the abdomen were normal. All laboratory parameters including alkaline phosphatase and liver enzymes, lactate dehydro-

genase, and serum calcium were within the normal range. Based on these results, the disease was classified as ISM.

Follow-Up of Serum Tryptase Levels

To exclude a transient increase in tryptase (following an anaphylactoid reaction) and to exclude an aggressive disease variant, the serum tryptase level was measured serially. In July 2003, the serum tryptase level amounted to 70.5 ng/ml. At the time of referral (January 2004), the serum tryptase concentration was 66.6 ng/ml. In February 2004, serum tryptase was found to be 71.0 ng/ml. Thus, no significant change in serum tryptase could be recorded, confirming an indolent subtype of SM.

Table 4. Evaluation of severe life-threatening anaphylactoid episodes with hypotension and shock in 40 patients with SM referred to the Vienna University Hospital between 1988 and 2004

Patient No.	f/m	WHO subtype	UP-like skin lesions	Serum tryptase ng/ml	Life-threatening hypotensive episodes		
					none	before SM diagnosed	after SM diagnosed
1	f	SM-AHNMD	no	11	+		
2	f	ISM	yes	55	+		
3	f	ISM	yes	48	+		
4	m	SSM	yes	937	+		
5	f	SM-AHNMD	yes	101	+		
6	f	SSM	yes	353	+		
7	m	ISM	yes	108	+		
8	f	ISM	yes	113	+		
9	f	ISM	yes	938			+(I)
10	m	ISM	yes	58	+		
11	m	ISM	yes	15	+		
12	f	SSM	yes	1,090			+(III)
13	m	ISM	yes	91	+		
14	m	ISM	yes	50	+		
15	f	ISM	yes	175			+(I)
16	f	ISM	yes	23			+(I)
17	m	ASM	no	54	+		
18	f	ASM-AHNMD	no	323	+		
19	f	ISM	yes	17	+		
20	f	ISM	yes	70	+		
21	f	SSM	yes	153	+		
22	m	ISM	yes	650	+		
23	m	ISM	yes	169			+(II)
24	f	ISM	yes	46			+(I)
25	m	ASM	no	285	+		
26	f	ASM	no	n.t.	+		
27	m	ISM	yes	170	+		
28	m	SM-AHNMD	no	89	+		
29	f	ISM	yes	26	+		
30	m	ISM	yes	17	+		
31	m	ISM	yes	20	+		
32 ^a	m	ISM	no	67		+(II)	
33	f	ISM	yes	18	+		
34	f	ISM	yes	47	+		
35	m	MCL	no	970	+		
36	m	ISM	yes	34	+		
37 ^b	m	ISM	yes	35		+(I)	
38	m	ASM-AHNMD	no	570	+		
39	m	ASM-AHNMD	no	305	+		
40	f	SM-AHNMD	yes	190	+		

The occurrence of life-threatening hypotensive episodes was analyzed retrospectively. SM = Systemic mastocytosis; ISM = indolent systemic mastocytosis; SSM = smoldering systemic mastocytosis; ASM = aggressive mastocytosis; AHNMD = associated clonal hematologic non-mast cell lineage disease; MCL = mast cell leukemia; UP-like = urticaria pigmentosa-like; n.t. = not tested. Frequency of severe episodes (score shown in brackets): grade I = <1 episode/year; grade II = 1–3 episodes/year; grade III = >3 episodes/year.

^a Present case: in this patient no skin lesions were found.

^b In this patient, a few UP-like skin lesions were detected after repeated severe episodes of hypotension had occurred and the patient was consequently referred to a dermatologist.

Final Diagnosis and Treatment Recommendations

The final diagnosis was ISM associated with severe mediator-related symptoms (ISM_{SY}). The patient was advised to avoid all potentially triggering factors and drugs, and to carry an epinephrine self-injector to be applied in case of an emergency (severe hypotensive episode). In addition, the use of oral anti-histamines on demand (i.e. in case of mediator-related symptoms) was recommended. Since no signs of aggressive disease were found, no other drugs were prescribed.

Frequency of Life-Threatening Events in Patients with SM

Based on the intriguing example of a severe anaphylactoid reaction as a first symptom in a patient with SM, we retrospectively examined 40 cases of SM seen between 1988 and 2004, for the occurrence of severe life-threatening anaphylactoid symptoms. In these examinations, we found that 20% of all patients with SM ($n = 8$) developed severe (life-threatening) anaphylactoid reactions (table 4). In 6 cases (15%), these symptoms occurred after the diagnosis of SM had been established (table 4). All these patients received prophylactic H₁ and H₂ antihistamines and were advised to carry an epinephrine self-injector to be used on demand. In 2 cases (5%), severe hypotensive episodes were recorded before the diagnosis of SM was established. In 1 of the 2 patients, a few small maculopapular skin lesions were detected and found to contain MC infiltrates on histological examination. In the 2nd patient (described in detail in the current report), no skin lesions were detected even after a repeated and thorough investigation of the entire skin surface.

The frequency of severe episodes recorded in the 8 patients examined, ranged from grade I (<1 severe episode/year) to grade III (>3 severe episodes per year; table 4). Interestingly, in these patients, reactions to insects (usually hymenoptera) were identified as a major trigger inducing anaphylactoid episodes. Similarly, in the case presented in detail in this report, reactions to ant bites and yellow jacket stings were recognized as primary triggers leading to severe hypotensive reactions.

Discussion

SM is a heterogenous disease with regard to the clinical course and occurrence of mediator-related symptoms [1–4]. Such symptoms can develop in any category of SM and can represent a serious clinical problem [22–28]. In those patients who do not show typical skin lesions, these symp-

toms may be confused with allergies, endocrinologic disorders, or other internal diseases [28]. We report a patient with severe anaphylactoid reactions to hymenoptera stings and ant bites, in whom allergy tests were negative and no typical skin lesions were found. The diagnosis of SM was suspected in this patient because of an elevated serum tryptase level, and was confirmed by an investigation of the bone marrow.

The serum tryptase level is a well-established and valuable screening test for patients with suspected SM [16, 17, 21, 28]. In fact, almost all patients with SM have a serum tryptase level exceeding 20 ng/ml [16, 17, 21, 33]. One exception to this rule is bone marrow mastocytosis, a special subvariant of SM in which mastocytosis infiltrates are detected in the bone marrow but not in the skin [2]. In these patients, tryptase levels are often below 20 ng/ml [21]. In most other patients with mastocytosis involving the bone marrow, however, tryptase levels are elevated [16–21]. In our patient, the serum tryptase level was used as a screen marker to search for mastocytosis and was indeed found to be elevated. In a consecutive examination of the bone marrow, the diagnosis of SM was established.

The major criterion of SM is the 'positive' histology in a visceral organ [20, 21]. In almost all cases, the bone marrow is examined to exclude or to document the existence of such infiltrates in patients with suspected SM [12–14]. In our patient we were also able to establish the diagnosis of SM by a histologic and immunohistochemical examination of the bone marrow. In these analyses, bone marrow MCs were found to form focal aggregates (major criterion) and to stain positive for tryptase, *kit*, and CD9 which is consistent with the MC phenotype [34]. Minor criteria of SM relate to the morphology of MCs, expression of CD2 and CD25 in/on MC, the *c-kit* mutation D816V, and an elevated serum tryptase level (>20 ng/ml) [19, 20]. If at least one major and one minor or three minor criteria are fulfilled, the SM diagnosis can be established [19, 20]. In our patient, all these criteria were met. One of these criteria, i.e. elevated tryptase, was already known before the bone marrow biopsy was performed. Nevertheless, it was important to establish the diagnosis of SM by bone marrow examination, because an elevated serum tryptase level is also found in other myeloid neoplasms apart from SM [35–37]. Moreover, serum tryptase may also increase during and after an anaphylactic episode – and even when measured several days after an attack, enzyme levels may not have returned to baseline yet [23–28]. Therefore, in these patients, it is recommended to repeat the test several weeks following such an

episode. If then, as in our patient, serum tryptase is still elevated, the likelihood of SM is high [17, 28].

A well-known clinical paradox is that patients with ASM and MCL usually lack urticaria pigmentosa-like skin lesions [19, 20, 38, 39]. In contrast, patients with isolated bone marrow mastocytosis, in whom skin lesions are also absent, are considered to have a favorable prognosis [2, 19, 20]. As mentioned above, these patients usually present with a normal or only slightly elevated serum tryptase concentration [21]. In our patient, however, the serum tryptase level was clearly elevated so that an aggressive disease variant had to be excluded. In fact, it was of considerable importance to exclude organopathy with consecutive loss of organ function due to MC infiltrates (clinical findings) [19, 20, 39]. In addition it was of importance to follow up this patient during the next few months in order to recognize or exclude progression of SM. In this follow-up, the serum tryptase was found to be at a constant level of about 60–70 ng/ml. This observation was in favor of a stable disease course and argued against an aggressive disease variant. Also, no other clinical or laboratory signs of aggressive MC disease were found.

A number of different explanations for the unusual constellation in our patient (indolent disease despite absence of skin lesions in a patient with elevated tryptase) have to be considered. First, it may well be that the disease process in our patient was not restricted to the bone marrow but was also involving other internal organs which resulted in an elevated tryptase level. A second possibility may be that the number of MC was low (as in other patients with bone marrow mastocytosis), but tryptase was constantly secreted at high levels from MC. Other alternatives would represent a decreased degradation of the enzyme or decreased elimination from the blood. The possibility of an associated clonal hematologic non-MC lineage disease in the bone marrow as a source of 'extra-tryptase', could be excluded.

The occurrence of severe life-threatening mediator-related symptoms in patients with mastocytosis is a well-known phenomenon [22–26]. Usually, such symptoms may develop in patients in whom mastocytosis had already been diagnosed (because of urticaria pigmentosa-like skin lesions). In a retrospective analysis of a representative cohort of our own patients, we found that approximately 15% of these SM patients develop life-threatening hypotensive episodes. In 2 patients, these symptoms were recorded before the diagnosis of SM could be established. This is of great importance because prompt medical care and appropriate therapy are required in these cases. In our patient the disease apparently could not be diagnosed

before mediator-related events occurred because of the absence of skin lesions. From this case and other similar cases it may thus be concluded that in all patients with unexplained attacks of severe hypotension or shock or unexplained severe anaphylactoid reactions to insects, the serum tryptase level should be measured and the bone marrow examined for the presence of MC infiltrates.

An interesting aspect in patients with SM is that life-threatening anaphylactoid episodes after hymenoptera stings occur in the absence of any measurable specific IgE or other clinical or laboratory signs of an allergic disease [23–26]. This remarkable phenomenon may have several explanations. First, these patients may have extremely low levels of specific IgE in their serum, but still have enough MC-bound IgE to cause anaphylactic reactions. Another explanation would be that insect compounds are able to directly activate neoplastic MC in SM. However, it remains unknown why these patients particularly exhibit severe responses against hymenoptera.

After the SM diagnosis (subvariant ISM) had been established in our patient, a treatment plan was set up including H₁ and H₂ antihistamines and an epinephrine pen self-injector to be used in case of an emergency. In addition, the patient was advised to avoid all potential triggers of MC activation.

In summary, the case described here shows that the absence of skin lesions does not exclude the diagnosis of ISM even if the serum tryptase level is clearly elevated. Moreover, our case confirms that in patients with recurrent anaphylactoid reactions to insects without overt allergy, mastocytosis is an important differential diagnosis to be considered.

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