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Original Article

Fatal Anaphylaxis to Yellow Jacket Stings in Mastocytosis: Options for Identification and Treatment of At-Risk Patients

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What is already known about this topic? Although patients with indolent systemic mastocytosis (ISM) are at an extremely high risk for severe and recurrent systemic reactions to yellow jacket (YJ) stings, demonstration of sensitization is especially challenging because YJ venom specific IgE (sIgE) levels are regularly reported below 0.35 kU_A/L.

What does this article add to our knowledge? Without immunotherapy, 97.5% experience a resystemic reaction, of which 90.6% are severe. The current reference value of 0.35 kU_A/L yields a sensitivity of 77.6% while the optimal diagnostic accuracy is achieved at 0.17 kU_A/L.

How does this study impact current management guidelines? Our data show the need for regular sIgE screening and an adjusted lower clinical threshold of YJ venom sIgE in patients with ISM. We recommend discussing the possibility of venom immunotherapy with all patients with ISM with YJ venom sIgE above the proposed cutoff.

BACKGROUND: Patients with indolent systemic mastocytosis (ISM) are at risk for severe anaphylactic reactions to yellow jacket (YJ) stings while demonstration of sensitization can be challenging because specific IgE (sIgE) levels are regularly below 0.35 kU_A/L. The implication of missing YJ allergy is illustrated by a case of fatal anaphylaxis.

OBJECTIVE: To explore the natural course of YJ venom allergy and the diagnostic accuracy and therapeutic consequence of YJ venom sIgE in patients with ISM.

METHODS: All patients with ISM seen from 1981 to 2015 (n = 243) were evaluated on the number of YJ stings, reaction severity, and sensitivity and specificity of YJ venom sIgE. YJ venom allergic patients without mastocytosis served as control (n = 313).

RESULTS: A total of 153 patients with ISM were stung during adult life. The first systemic reaction was more often severe in patients with ISM than in patients without mastocytosis (69.9% vs 22.0%) and reactions recurred in 40 of 41 re-stung patients with ISM. ISM reactors showed lower YJ venom sIgE levels than nonmastocytosis reactors (0.61 vs 4.83 kU_A/L; $P < .001$) and asymptomatic sensitization was exceedingly rare. In ISM the current clinical threshold of 0.35 kU_A/L yields a sensitivity and specificity of 77.6% and 87.5%, respectively. The optimal diagnostic accuracy is achieved at 0.17 kU_A/L (sensitivity, 83.6%; specificity, 85.0%).

CONCLUSIONS: The high rate of severe reactions and the fatal case underscore the importance of adequate diagnostic sensitivity of sIgE in patients with ISM. The sensitivity of sIgE can be ameliorated by lowering the threshold to 0.17 kU_A/L, retaining good specificity. We recommend sIgE screening in all patients with ISM and discussing immunotherapy when YJ venom sIgE exceeds 0.17 kU_A/L. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1264-71)

Key words: *Indolent systemic mastocytosis; Yellow jacket; Hymenoptera; Specific IgE; Ves v 5; Sensitization*

Patients with indolent systemic mastocytosis (ISM) represent a particular risk group for severe and occasionally fatal anaphylactic reactions to yellow jacket (YJ) stings, occurring in nearly half of the patients stung in adult age.[1-4] This risk is far higher compared with patients without mastocytosis in whom it does not exceed 3%.[5] ISM is the most prevalent form of systemic mastocytosis and is characterized by a clonal proliferation of abnormal mast cells in extradermal tissues.[6] The clinical severity

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Abbreviations used
AUC- Area under the curve
ISM- Indolent systemic mastocytosis
MH- Methylhistamine
MIMA- Methylimidazole acetic acid
Ves v 5- Vespula vulgaris *antigen 5*
sIgE- Specific IgE
VIT- Venom immunotherapy
YJ- Yellow jacket

of anaphylaxis presumably relates to excessive mast cell mediator release (eg, histamine) by the abundant number of aberrant mast cells.[6]

When no systemic reactions have occurred yet, patients with ISM are prescribed an epinephrine autoinjector as a precaution, though the only preventive therapy available to reduce the risk of future systemic reactions is venom immunotherapy (VIT). VIT is potentially lifesaving in patients with ISM, but should be implemented only after careful consideration because it is advised to be maintained lifelong.[7] In practice, only patients with ISM who have already had at least 1 anaphylactic episode are treated with VIT. The unmet need for identification and treatment of patients with ISM at risk for a first-time anaphylactic reaction to YJ stings became forcefully clear to us after a case of a fatal reaction.

CASE OF FATAL ANAPHYLACTIC REACTION TO YJ VENOM

A 58-year-old female patient was diagnosed with ISM 8 years previously on the basis of elevated baseline serum tryptase level (56.7 μg/L), urticaria pigmentosa confirmed by skin biopsy, and mast cell infiltrates in bone marrow. YJ stings 8 and 6 years previously had not elicited an allergic reaction and specific IgE (sIgE) level was not elevated (<0.01 kU_A/L) 3 years before the anaphylactic reaction. On the day of the anaphylactic reaction, she was stung in the neck, chest, and wrist by 1 YJ after which she felt light-headed within 2 minutes, developed difficulty in breathing, and collapsed 4 minutes after being stung. The ambulance personnel arrived 7 minutes after the first symptoms appeared and immediately administered 0.5 mg epinephrine intramuscularly during the course of which her pulse became impalpable. Basic life support was started and an intravenous line was established for administration of epinephrine by continuous infusion as well as a second line for administration of clemastine and dexamethasone. Intubation was initially unsuccessful because of swelling of the tongue, but succeeded after 15 minutes. The total reanimation lasted 28 minutes, with 17 minutes of asystole and 8 mg intravenous epinephrine administration. After hemodynamic stabilization, the patient was transferred to the intensive care unit. She did not regain consciousness. On the fifth day, the diagnosis of cerebral death was established and treatment was stopped. The patient's husband stated that 2 months before the fatal reaction she had developed a large local reaction following a sting without any systemic symptoms. On admission, positive sIgE against YJ venom (0.51 kU_A/L) and *Vespula vulgaris* antigen 5 (Ves v 5; 2.31 kU_A/L) were found in serum samples. Massive mast cell degranulation was evident from high levels of serum tryptase (1836 μg/L), urinary methylhistamine (MH; 468 μmol/mol creatinine), and methylimidazole acetic acid (MIMA; 8.2 mmol/mol creatinine). sIgE levels to YJ venom and Ves v 5 measured 4 days after the sting were further elevated (0.78 kU_A/L and 4.77 kU_A/L, respectively), while tryptase level was relatively low (17.4 μg/L) probably due to mast cell exhaustion.

The particulars of this case led us to several research questions: what is the natural course of YJ venom allergy in patients with mastocytosis? Should we have checked for sensitization to YJ following the large local reaction 2 months earlier? Should the presence of sIgE against YJ venom have led us to consider preventive VIT in light of the natural course of the disease? And if so, what are the diagnostic characteristics and optimal clinical cutoff points of sIgE to YJ venom and its major allergen Ves v 5 in serum? To answer these questions, we retrospectively analyzed the data of all our patients with ISM regarding their history of YJ venom allergy, and the diagnostic accuracy of sIgE in such patients who could recall ever having been stung by a YJ. The sensitivity of sIgE was compared with patients with a YJ venom allergy not suspected of mastocytosis.

METHODS

Subjects

The ISM cohort consisted of all consecutive adult patients with ISM seen at University Medical Center Groningen (1981-2015) who were seen either because of a systemic reaction to a YJ sting and/or because of other symptoms of ISM (eg, urticaria pigmentosa or flushing). From every patient, a history of YJ stings was established from the patients' charts or telephone interviews. Because patients with ISM were not treated with VIT between 1990 and 2009,[3] the natural course of sting reactions could be evaluated in addition to the diagnostic accuracy of sIgE. The diagnosis of ISM was established according to the World Health Organization criteria.[8]

The nonmastocytosis cohort consisted of all adult patients seen because of a systemic reaction to a YJ sting (2009-2015) and a serum tryptase level of less than 10.0 μg/L, urinary MH level of 154 μmol/mol creatinine or less, and absence of clinical skin lesions compatible with urticaria pigmentosa. For study purposes, the cutoff point for tryptase was set at 10.0 μg/L because the risk of systemic mastocytosis is very low below this value.[9]

The diagnosis of YJ venom allergy was based on internationally accepted clinical criteria and systemic reactions were classified according to Müller.[5,10] Grade I reactions were considered as mild, grades II to III as moderate, grade IV without incontinence or loss of consciousness as severe, and grade IV with incontinence or loss of consciousness or death as very severe. The local medical ethics committee deemed that official medical ethical approval was not required.

YJ venom sensitization and mast cell parameters

If sIgE was not measured for clinical purposes, stored serum samples from a date closest to the last systemic reaction or YJ sting were analyzed for sIgE against YJ venom and Ves v 5 using the fluoro-enzyme-immunoassay Phadia ImmunoCAP (Phadia, Uppsala, Sweden). Intracutaneous tests were used in only those patients with a history positive for anaphylaxis but negative in serological testing. Stepwise incremental concentrations of 0.03 mL venom were used ranging from 0.001 to 1 μg/mL, with a positive histamine solution control and a negative physiological saline solution control. A positive test result was defined as a wheal of 5 mm or more with surrounding erythema.

Serum tryptase levels were determined with the B_{12} assay,[11] using ImmunoCAP Tryptase reagents and the Phadia 250 analysis device (Thermo Fisher Scientific, Uppsala, Sweden). The interassay analytical coefficient of variation in our laboratory is 5.8%. Tryptase concentrations of more than 10.0 μg/L were verified for interference by heterophilic antibodies and corrected tryptase concentrations were used.[12]

To obtain MH and MIMA values, urine samples were collected in containers with a small amount of chlorhexidine after an overnight fast, discarding the first voiding after wakening. Subjects were asked to refrain from histamine-rich foods and drinks for 24 hours before urine collection. Levels of MH and MIMA were determined by an isotope-dilution mass fragmentographic method.[13,14] In healthy subjects, the mean ± SD is 101 ± 33 (50-154) μmol/mol creatinine and 1.3 ± 0.3 (0.9-1.9) mmol/mol creatinine, respectively.[15] The interassay analytical coefficient of variation in our laboratory is 6.8% for MH and 4.2% for MIMA.

Bone marrow examinations

The indication for bone marrow and c-KIT mutation analysis was based on a clinical suspicion of systemic mastocytosis, either due to the presence of skin lesions or tryptase level of more than 10 μg/L.[9] Bone marrow examination was performed as previously described.[16] Briefly, bone marrow biopsies were taken from the iliac crest and examined for the presence of multifocal clusters or cohesive aggregates/infiltrates of more than 15 mast cells and atypical morphology of mast cells by tryptase and CD117 staining (using primary antibodies anti-mast cell tryptase, clone AA1 [Dakocytomation, Glostrup, Denmark] and affinity-isolated polyclonal rabbit anti-human CD117 [Dakocytomation]). Bone marrow aspirates were recovered in EDTA and smears were stained for May-Grunwald-Giemsa and toluidine blue. MCs were analyzed outside the marrow particles and atypical morphology was recorded.

Immunophenotyping. For bone marrow MC immunophenotyping, 300,000 events were analyzed using 4-color staining with CD45-peridin-chlorophyl protein/cyanine 5.5, CD117-allophycocyanine, CD2-phycoerythrin, and CD25-fluorescein isothiocyanate (all derived from Becton Dickinson Biosciences, San Jose, Calif). Expression of CD2 and CD25 was measured on CD45-positive/bright CD117-positive MCs with the isotype pattern used as control. The results were analyzed on a FacsCalibur flow cytometer (Becton Dickinson Biosciences) using WINLIST 5.0 software.

C-KIT mutation analysis. To detect the KIT D816V mutation, RNA was initially isolated from EDTA-anticoagulated bone marrow cells with the QIAampRNA Blood MINI Kit (QIAGEN, Westburg, Leusden, the Netherlands). C-DNA was synthesized using the Promega Reverse Transcriptase kit (Promega Benelux, Leiden, the Netherlands) and amplified using previously described primers.[17,18] The resulting 346-bp PCR product was digested with Hae III en Hinf I (BioLabs, Westburg, Leusden, the Netherlands) to detect the wild-type and the D816V mutation by agarose gel electrophoresis. From December 2007, detection of the KIT-D816V mutation was performed with a real-time PCR using previously described primers 5′-TTGTGATTTTGGTCTAGCCAGACT-3′ and 5′-GTGCCATCCACTTCACAGGTAG-3′.[19] Since the use of this more sensitive technique, the D816V mutation was found in all patients with ISM.

Statistical methods

Statistical analysis was performed with IBM Statistics 22.0 (SPSS, Armonk, NY). Categorical variables were expressed as percentage and metric variables as mean ± SD or as median and interquartile range as appropriate. Group differences were tested using the independent samples *t* test and Mann-Whitney *U* test. Percentages were compared using the chi-square test. The optimal threshold for sIgE against YJ venom and Ves v 5 to differentiate between patients with and without a history of clinical reactivity was determined by receiver-operator characteristic curves. Areas under the curve (AUCs) of less than 0.70 were interpreted as poor accuracy, $0.70 < AUC < 0.90$ as moderate accuracy, and AUC of more than 0.90 as high accuracy.[20] The cutoff points were selected on the greatest combined sensitivity and specificity, with a minimum specificity of 80%. *Sensitivity* was defined as the percentage of tests exceeding the cutoff point obtained from patients with a history of clinical reactivity. *Specificity* was defined as the percentage of negative test results obtained from patients without clinical reactivity. *P* values of less than .05 were considered to be statistically significant.

RESULTS

Characteristics of ISM cohort and reactions to YJ stings

Between 1981 and 2015, 243 adult patients with ISM were seen at the University Medical Center Groningen of whom 153 (63%) experienced a YJ sting at least once during adulthood. Of these 153 patients, 83 (54.2%) ultimately developed a systemic reaction. An overview of the patient selection procedure, number of stings per patient, and systemic reactions is shown in Figure 1, and characteristics of the final study group are presented in Table I.

On average, patients with a systemic reaction experienced a comparable number of stings as patients without a systemic reaction (Figure 1; 147 stings in 83 patients = 1.77 vs 134 stings in 70 patients = 1.91). Patients with systemic reactions were older at the time of the index sting than were patients without systemic reactions (51.3 vs 45.5 years; $P = .005$), had urticaria pigmentosa less often (43.4% vs 81.4%; $P < .001$), and showed higher levels of YJ venom sIgE (0.62 vs 0.01 kU_A/L; $P < .001$) and Ves V 5-sIgE (0.40 vs 0.01 kU_A/L; $P < .001$), but also had a shorter time interval between the index sting and sIgE sampling (7.2 vs 21.0 months; $P < .001$). No differences could be found in total levels of IgE or in tryptase, MH, or MIMA levels.

An overview of the severity of sting reactions is provided in Table II. The first systemic sting reaction was very severe in 69.9% (n = 58), severe in 16.9% (n = 14), moderate in 7.2% (n = 6), and mild in 6.0% (n = 5) of the patients. One fatal reaction occurred. In the period before the initiation of VIT, systemic reactions recurred in 40 of 41 (97.5%) re-stung patients of which 58 of 64 (90.6%) reactions were severe. Overall, the most severe reaction was very severe in 84.3% (n = 70), severe in 13.3% (n = 11), and moderate in 2.4% (n = 2) of the patients. During follow-up, no fatal anaphylactic reaction occurred although 2 fatal anaphylactic reactions happened in our center outside the scope of this study after stopping VIT.[3]

Characteristics of nonmastocytosis cohort and reactions to YJ stings

Between 2009 and 2015, 313 adult patients with serum tryptase levels of less than 10.0 μg/L and urinary MH excretion of 154 μmol/mol creatinine or less were diagnosed with a

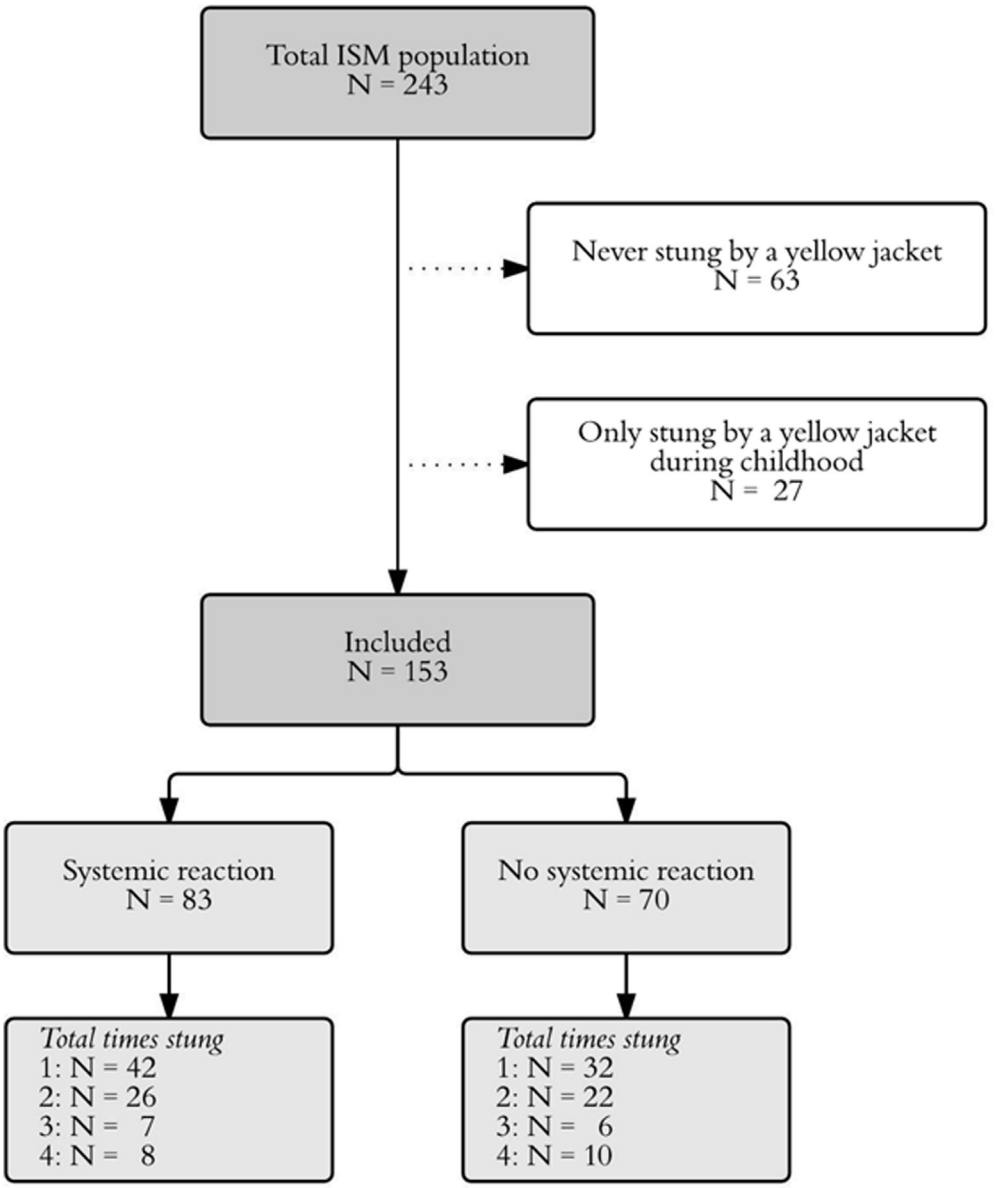

FIGURE 1. Flowchart of the patient selection procedure, systemic reactions, and total number of stings in patients with ISM.

systemic reaction following a YJ sting. An overview of the patient characteristics is provided in Table I. These patients had higher YJ venom sIgE levels than did patients with ISM with a systemic reaction (4.83 vs 0.62 kU_A/L; $P < .001$) but the time interval between sIgE sampling and the sting was also shorter (4.3 vs 7.2 months; $P < .001$). In addition, patients without mastocytosis showed higher total IgE levels (71.0 vs 20.9 kU_A/L; $P < .001$).

Overall, the first systemic reaction was less severe than the first reaction in patients with ISM: 22% (n = 69) presented with a very severe reaction, 25.6% (n = 80) with a severe reaction, 39.6% (n = 124) with a moderate reaction, and 12.8% (n = 40) with a mild reaction. Fatal anaphylaxis did not occur.

Diagnostic accuracy of sIgE against YJ venom in patients with ISM

Using the manufacturer's recommended clinical reference value for sensitization of 0.35 kU_A/L or more, positive YJ venom sIgE levels could be detected in 69.9% (n = 58) of patients with ISM with a history of a systemic reaction. In the remaining 25 patients, 18 underwent intracutaneous testing, which was positive in all cases. In 6 patients, intracutaneous testing was not performed because of very severe field reactions with loss of consciousness and incontinence, and 1 patient refused intracutaneous testing after a moderate sting reaction. In patients with ISM without systemic reactions, only 8.6% (n = 6) displayed YJ venom sIgE levels of 0.35 kU_A/L or more, making asymptomatic sensitization exceedingly uncommon, which underlines the clinical significance of sensitization in patients with mastocytosis.

The interval between the sting and sIgE sampling affected the level of sIgE. When the interval was 3 years or less, 79.7% (n = 55) of patients with ISM with a systemic reaction showed sIgE levels of 0.35 kU_A/L or more while levels were positive in only 21.4% (n = 3) when the interval exceeded 3 years. To eliminate the time effect and approach clinical practice, the

TABLE I. Clinical and biochemical characteristics of subjects with ISM and a history of a YJ sting

Characteristic / Reaction type	ISM		Nonmastocytosis
	Systemic	Not systemic	Systemic
No. of patients	83	70	313
Sex: male, n (%)	36 (43.4)	35 (50.0)	168 (53.7)
Urticaria pigmentosa, n (%)	36 (43.3)	57 (81.4)	0 (0.0)
Age at index sting (y)	51.3 ± 12.0	45.5 ± 12.9*	50.22 ± 14.1†
YJ venom sIgE (kU_A/L)	0.62 (0.15- 2.17)	0.01 (0.01- 0.04)*	4.83 (1.57-15.10)†,‡
Ves v 5 sIgE (kU_A/L)	0.40 (0.08- 1.52)	0.01 (0.01- 0.02)*	0.51 (0.11-0.71)†
Interval sting sIgE sampling (mo)	7.2 (3.2-30.8)	21.0 (8.1- 103.3)*	4.3 (2.3-8.6)†,‡
Total IgE (kU_A/L)	20.0 (10.6- 48.8)	14.4 (8.5- 33.5)	71.0 (36.0- 178.0)†,‡
Tryptase (μg/L)	24.2 (15.4- 39.8)	29.7 (17.0- 48.7)	4.8 (3.5-6.3)†,‡
MH (μmol/mol creatinine)	227 (166- 339)	235 (189-434)	93 (76-115)†,‡
MIMA (mmol/mol creatinine)	2.8 (2.3-3.9)	3.6 (2.4-5.2)	1.3 (1.2-1.7)†,‡
KIT D816V mutation analysis, n (%)			
Not indicated	—	—	313 (100.0)
Not performed	12 (14.4)	16 (22.9)	—
KIT D816V+	64 (77.2)	53 (75.6)	—
KIT D816V−	8 (9.4)	1 (1.4)	—

Data are presented as mean ± SD or median (interquartile ranges). Group differences were tested using the independent samples *t* test or Mann-Whitney *U* test.
*$P < .05$ between ISM systemic and nonsystemic reactors.
†$P < .05$ between ISM nonsystemic reactors and nonmastocytosis systemic reactors.
‡$P < .05$ between ISM systemic reactors and nonmastocytosis systemic reactors.

TABLE II. Natural course of reaction recurrence in patients with ISM

Reaction severity	First SR	First sting after first SR	Second sting after first SR	Third sting after first SR
No SR (n)	—	1	1	2
Grade I (n)	5	1	1	0
Grade II (n)	1	0	0	0
Grade III (n)	5	6	0	0
Grade IVa (n)	14	7	3	2
Grade IVb (n)	58	26	10	4
Total (n)	83	41	15	8

SR, Systemic reaction.
Reactions are classified according to Müller,[10] with separation of grade IV reactions into (a) severe and (b) very severe.

diagnostic accuracy of YJ venom sIgE was determined only in those patients in which the time interval between the sting and sIgE sampling was 3 years or less. This cohort comprised 69 patients with ISM with a systemic reaction and 43 patients with ISM without a systemic reaction. In these patients, receiver-operating characteristic analysis of YJ venom sIgE exhibited a high diagnostic accuracy in patients with ISM with an AUC of 0.90 (95% CI, 0.84-0.96; Figure 2). The current clinical reference value of 0.35 kU_A/L showed a sensitivity and specificity of 77.6% and 87.5%, respectively.

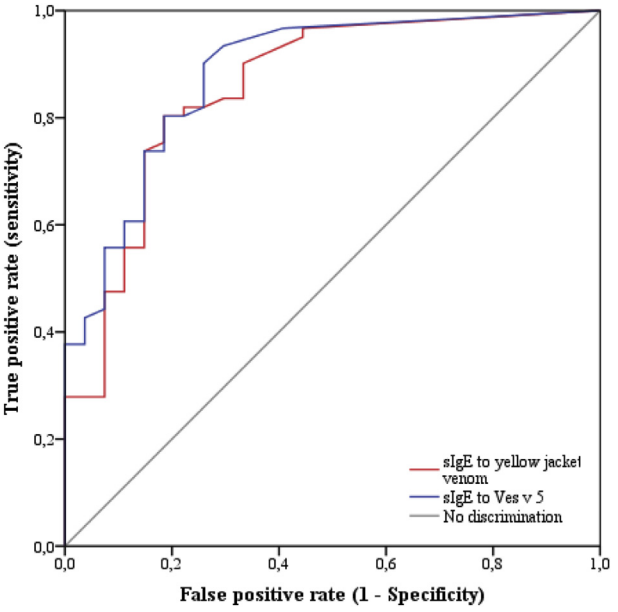

FIGURE 2. Receiver-operating characteristic curves for sIgE against YJ venom and Ves v 5 to assess the occurrence of systemic reactions in patients with ISM.

Effect of a lower cutoff value of sIgE on diagnostic accuracy in patients with ISM

The greatest combined sensitivity and specificity was found at a cutoff value of 0.21 kU_A/L, resulting in a sensitivity and specificity of 82.1% and 87.5%, respectively. To obtain an optimal sensitivity, the cutoff was lowered to 0.17 kU_A/L, resulting in a sensitivity and specificity of 83.6% and 85.0%, respectively. Using 0.35 kU_A/L as a reference value, positive YJ venom sIgE levels could be detected in 79.7% (n = 55) of patients with ISM with a history of a systemic reaction. Conversely, in patients with ISM without systemic reactions, only 11.6% (n = 5) displayed YJ venom sIgE levels of 0.35 kU_A/L or more. Using 0.17 kU_A/L as a reference value, positive YJ venom sIgE levels could be detected in 84.1% (n = 58) of patients with ISM with a history of a systemic reaction. Conversely, in patients with

ISM without systemic reactions, only 14.0% (n = 6) displayed YJ venom sIgE levels of 0.17 kU_A/L or more. In addition, in patients with ISM who could not recall ever being stung by a YJ and in those who were stung only during childhood, venom sIgE levels were all less than 0.17 kU_A/L (determined in 58 out of 90 patients). These results indicate that the clinical reference value of 0.35 kU_A/L can safely be lowered to increase the sensitivity due to the infrequency of asymptomatic sensitization in patients with ISM.

Diagnostic accuracy of Ves v 5 sIgE in patients with ISM

In the same subgroup, receiver-operating characteristic analysis of Ves v 5 sIgE showed the greatest combined sensitivity and specificity at a cutoff value of 0.11 kU_A/L, resulting in sensitivity and specificity of 80.3% and 81.5%, respectively (Figure 2). Using the more than 0.11 kU_A/L clinical cutoff point, additional Ves v 5 sIgE measurement correctly identified sensitization in 5 of 11 patients with ISM with a systemic reaction and a YJ venom sIgE of 0.17 kU_A/L or less, indicating a role for Ves v 5 sIgE in diagnosing YJ venom allergy in patients with ISM with negative YJ venom sIgE results.

Sensitization in systemically reacting patients without mastocytosis

In patients without mastocytosis who experienced a systemic reaction, YJ venom sIgE levels of 0.35 kU_A/L or more could be detected in 94.2% (n = 295). Sensitization to YJ venom could be demonstrated by positive intracutaneous skin test results in all patients with a negative sIgE outcome. In the subgroup of patients in which sIgE was measured within 3 years, the positive sIgE rate was only slightly higher than in the overall group (94.8%, n = 272). In contrast to patients with ISM, 87.5% showed sIgE levels above the threshold of 0.35 kU_A/L when the interval exceeded 3 years.

DISCUSSION

Fatal anaphylactic reactions due to insect venom allergy are fortunately rare, but the social impact of such a reaction is high. These fatalities often occur on the first systemic reaction. The case of a fatal anaphylactic reaction in a patient with ISM with a prior large local reaction and evidence of sensitization to YJ venom prompted us to question whether this fatal reaction could have been prevented by screening for sensitization and whether we therefore should recommend routine sensitization screening after every insect sting in patients with mastocytosis. Comparing our cohorts of patients with and without mastocytosis to those found in the literature, we conclude that systemic reactions in patients with ISM do not only occur more often than in the general population (34.2% [82 of 243] vs 3.0%[5]), but are also far more often very severe at the first systemic reaction (69.9% vs 22.0%) and have a higher recurrence rate when not treated by VIT (97.5% vs 50%[21]).

The high prevalence of YJ venom allergy in patients with ISM is probably a slight overestimation because other patients with ISM with subtle or absent symptoms of ISM may easily be missed.[22] Nevertheless, the prevalence of YJ-induced anaphylaxis is strikingly higher than that found in the general population, but similar to that previously reported in patients with ISM (25.0%).[23] In addition, we showed that once stung, the risk rises to 54.0% (83 of 153). Sensitization without a history of clinical reactions is found in 18.8% to 38.1% of the general population and poses a risk of a future systemic reaction in only 5.3% to 17.0%.[24-29] We found that asymptomatic sensitization is rare in patients with ISM and occurs in only 8.6% to 13.0%, depending on the cutoff point. Conversely, symptomatic sensation occurred in 34.2% of patients with ISM, indicating a large number of potentially preventable reactions. If we would have been aware of sensitization in the described case, should this have led to some form of intervention? It is questionable whether an autoepinephrine injector would have sufficed in light of the rapid and dramatic course of the reaction. Would prophylactic VIT have been an option? Although our findings suggest that sensitization is more strongly associated with systemic reactions in patients with ISM, the consequences on future reaction risk remain uncertain because prospective analysis is hard to achieve because of the rarity of the disease, the infrequent occurrence of YJ stings, and the strong contraindication against diagnostic sting challenges in patients with ISM.

Next to significantly more severe reactions and resystemic reactions, the baseline frequency of systemic reactions in stung patients with ISM is about 50% and comparable to the risk of resystemic reactions for current nonmastocytosis VIT-eligible patients, which supports the notion that these patients should be eligible for treatment.[30] We feel that preventive treatment should be discussed with all patients with ISM with elevated YJ venom sIgE wherein special attention should be paid to the estimated risks of a re-sting, the current uncertainty of the risk of a systemic reaction, the effects and burdens of VIT, and the necessity of lifelong treatment to maintain efficacy. Therefore, we feel that patients with ISM who suffer from a YJ sting should be recommended to undergo sensitization screening, both to identify potential patients at risk and to gather data on the implications of sensitization. The costs of these recommendations are relatively low because re-stings occur only once per 3.75 to 7.5 years, depending on the patient's occupation.[31]

Pivotal for these recommendations is the use of an optimal clinical reference value for YJ venom sIgE. Patients with ISM are known to demonstrate lower sIgE and total IgE levels, as was also found in our study, which is presumably due to the adsorption of sIgE to the surface of the expanded mast cell population resulting in less detectable free IgE. This is the first study to assess both the sensitivity and specificity of sIgE against YJ venom and Ves v 5 in a large data set of adult patients with ISM. Only 1 other study has evaluated the current threshold of 0.35 kU_A/L in patients with mast cell disorders and advised to lower the reference value to 0.10 kU_A/L.[32] In that study including 17 patients with systemic mastocytosis and 36 patients with other forms of mastocytosis or increased serum tryptase levels, the diagnostic sensitivity of sIgE was 87.7% at a threshold of 0.35 kU_A/L or more and could be elevated to 91.8% using a cutoff of 0.10 kU_A/L. However, the specificity was not taken into account. Applying the same threshold of 0.10 kU_A/L in our patients with ISM, we find not only a sensitivity increase of 77.6% to 85.0% but also a substantial specificity decrease of 87.5% to 77.5%.

The optimal combined diagnostic sensitivity and specificity of sIgE was found at a cutoff level of 0.21 kU_A/L (82.1% and 87.5%, respectively). However, because missing the diagnosis of YJ venom allergy could have serious consequences, a lower cutoff level of 0.17 kU_A/L is preferable, resulting in a sensitivity and specificity of 83.6% and 85.0%, respectively. This lower threshold poses no technical problems because sIgE levels can be

reliably measured above the detection limit of 0.10 kU_A/L.[33] Remarkably, the diagnostic accuracy at 0.17 kU_A/L equals the diagnostic accuracy of sIgE reported in patients without ISM.[34,35] Of note, the time interval between the sting and sIgE sampling seems more important to the level of sIgE in patients with ISM than in patients without mastocytosis, because only a minority of patients with ISM show positive sIgE levels after 3 years while most patients without mastocytosis are still sensitized. The lower levels of circulating sIgE might be an effect of an increased uptake of IgE by the abundant number of mast cells in mastocytosis.[36,37]

The diagnostic accuracy of Ves v 5 sIgE was lower than that of YJ venom sIgE in patients with ISM. In agreement with a previous report demonstrating improved sensitivity when adding Ves v 5 sIgE,[35] Ves v 5 sIgE improves the diagnostic accuracy of YJ venom sIgE when these are combined in patients with YJ venom sIgE levels of 0.17 kU_A/L or less. Considering the high costs of the Ves v 5 sIgE determination, we feel that measurement should be limited to establish sensitization in patients with a clear history of reactivity but YJ venom sIgE levels of 0.17 kU_A/L or less.

In conclusion, the high diagnostic accuracy of YJ venom sIgE in patients with ISM who have been stung (AUC, 0.90) supports its use as a screening tool. In light of a recent fatal reaction, we recommend sIgE screening before a sting happens and after every YJ sting for all patients with ISM to identify development of sensitization and those at risk. In addition, the optimal threshold for the diagnosis of YJ venom allergy is found at a reference value of 0.17 kU_A/L (sensitivity, 83.6%, and specificity, 85.0%) and determination of Ves v 5 sIgE should be limited to establish sensitization in patients with a clear history of reactivity but YJ venom sIgE levels of 0.17 kU_A/L or less. Finally, on the basis of the relatively low rate of asymptomatic sensitization and the high prevalence of severe systemic reactions in patients with ISM, we recommend discussing the possibility of VIT with all patients with ISM exhibiting elevated YJ venom sIgE levels, even if they are hitherto asymptomatic, in order to arrive at an optimal individualized management strategy.

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