Hymenoptera venom allergy
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Fatal anaphylaxis to yellow jacket stings in mastocytosis: options for identification and treatment of at risk patients

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Chapter 3

ABSTRACT

Background: Patients with indolent systemic mastocytosis (ISM) represent a particular risk group for severe, sometimes fatal anaphylactic reactions to yellow jacket (YJ) stings. However, demonstration of sensitization can be challenging as slgE levels are regularly reported below 0.35 kU/L. The implication of missing YJ allergy in ISM patients is illustrated by a case of fatal anaphylaxis.

Objective: To explore the history of YJ venom allergy and the diagnostic accuracy of YJ venom-slgE in patients with ISM.

Methods: All ISM patients seen from 1981-2015 (n = 243) were evaluated on number of YJ stings, reaction occurrence with corresponding severity, and natural course of reaction recurrence. Sensitivity and specificity of YJ venom-slgE was analyzed. YJ venom allergic non-mastocytosis patients served as control group (2009-2015; n = 313).

Results: 153 ISM patients were stung during adult life. The first systemic reaction was very severe in 58 of 83 (69.9%) ISM patients compared to 69 of 313 (22.0%) non-mastocytosis patients. ISM reactors showed lower YJ venom-slgE levels than non-mastocytosis reactors (0.61 vs. 4.83 kU/L; P < .001). In ISM patients, the current clinical reference value of 0.35 kU/L yields a sensitivity and specificity of 77.6% and 87.5%, respectively, while the most optimal diagnostic accuracy is achieved at 0.17 kU/L (sensitivity 83.6%, specificity 85.0%). Without immunotherapy, systemic reactions recurred in 40 of 41 (97.5%) re-stung patients of which 58 of 64 (90.6%) reactions were severe.

Conclusions: The high rate of severe reactions underscores the importance of adequate diagnostic sensitivity of slgE in ISM patients. The low sensitivity of slgE at the current threshold can be overcome by lowering the reference value to 0.17 kU/L, while retaining good specificity.
INTRODUCTION

Indolent systemic mastocytosis (ISM) patients 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 to non-mastocytosis patients where 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 extra-dermal tissues.\(^6\) The clinical severity of anaphylaxis presumably relates to excessive mast cell mediator release (e.g. histamine) by the abundant number of aberrant mast cells.\(^6\)

When no systemic reactions have occurred yet, ISM patients are prescribed an epinephrine auto-injector 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 ISM patients, but should only be implemented after careful consideration because it is advised to be maintained lifelong.\(^7\) In practice, only ISM patients that have already had at least one anaphylactic episode are treated with VIT. The unmet need for identification and treatment of ISM patients 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 yellow jacket venom

A 58-year-old female patient was diagnosed with ISM eight years previously based on elevated baseline serum tryptase (56.7 µg/L), urticaria pigmentosa confirmed by skin biopsy, and mast cell infiltrates in bone marrow. YJ stings eight and six years previously had not elicited an allergic reaction and specific (s)IgE was not elevated (< 0.01 kU\(_A\)/L) three years before the anaphylactic reaction. On the day of the anaphylactic reaction, she was stung in the neck, chest and wrist by one YJ after which she felt light-headed within two minutes, developed difficulty in breathing and collapsed four minutes after being stung. The ambulance personnel arrived seven 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 two 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 acetate acid (MIMA; 8.2 mmol/mol creatinine). SlgE to YJ venom and Ves v 5 measured four days after the sting were further elevated (0.78 kUA/L respectively 4.77 kUA/L), while tryptase was relatively low (17.4 ug/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 mastocytosis patients? Should we have checked for sensitization to YJ following the large local reaction two months earlier? Should the presence of slgE 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 cut-off points of slgE to YJ venom and its major allergen Ves v 5 in serum? To answer these questions, we retrospectively analyzed the data of all our ISM patients regarding their history of YJ venom allergy, and the diagnostic accuracy of slgE in such patients who could recall ever having been stung by a YJ. The sensitivity of slgE was compared to patients with a YJ venom allergy not suspected of mastocytosis.

**METHODS**

**Subjects**

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

The non-mastocytosis cohort consisted of all adult patients seen because of a systemic reaction to a YJ sting (2009-2015) and a serum tryptase level < 10.0 µg/L, urinary MH ≤ 154 µmol/mol creatinine, and absence of clinical skin lesions compatible with urticaria pigmentosa. For study purposes, the cut-off 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, grade II-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 only used in 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 was defined as a wheal ≥ 5 mm with surrounding erythema.

Serum tryptase levels were determined with the B12 assay, using ImmunoCAP Tryptase reagents and the Phadia 250 analysis device (Thermo Fisher Scientific, Uppsala, Sweden). The inter-assay analytical coefficient of variation in our laboratory is 5.8%. Tryptase concentrations > 10.0 μg/L were verified for interference by heterophilic antibodies and corrected tryptase concentrations were used.

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. In healthy subjects, the mean ± standard deviation is 101 ± 33 (50–154) μmol/mol creatinine and 1.3 ± 0.3 (0.9–1.9) mmol/mol creatinine, respectively. The inter-assay 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 > 10 μg/l.

Briefly, bone marrow biopsies were taken from the iliac crest and examined for the presence of multifocal clusters or cohesive aggregates/infiltrates of > 15 mast cells and atypical morphology of mast cells by tryptase and CD117 staining (using primary antibodies anti-MC 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-Grünwald-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 four-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, CA, USA). 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 QIAamp®RNA 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'.\(^{19}\)

**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 ± standard deviation 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 (AUC) < 0.70 were interpreted as poor accuracy, 0.70 < AUC < 0.90 as moderate accuracy, and AUC > 0.90 as high accuracy.\(^{20}\) The cut-off 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 cut-off point obtained from patients with a history of clinical reactivity. Specificity was defined as the percentage of negative tests obtained from patients without clinical reactivity. \(P\) values < .05 were considered to be statistically significant.

**RESULTS**

**Characteristics of ISM cohort and reactions to YJ stings**
Between 1981 and 2015, 243 adult ISM patients 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 shown in Table 1.
Yellow jacket stings in mastocytosis: options for identification and treatment

Total ISM population
n = 243

Never stung by a yellow jacket
n = 63

Only stung by a yellow jacket during childhood
n = 27

Included
n = 153

Systemic reaction
n = 83

No systemic reaction
n = 70

Total times stung
1) n = 42
2) n = 26
3) n =  7
4) n =  8

Total times stung
1) n = 32
2) n = 22
3) n =  6
4) n = 10

Figure 1 | Flowchart of the patient selection procedure, systemic reactions and total number of stings in indolent systemic mastocytosis (ISM) patients.

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 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/L; \( P < .001 \)) and Ves V 5-sIgE (0.40 vs. 0.01 kU/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.
Table 1 | Clinical and biochemical characteristics of subjects with indolent systemic mastocytosis (ISM) and a history of a yellow jacket sting.

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>ISM</th>
<th>Non-mastocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systemic</td>
<td>Not systemic</td>
</tr>
<tr>
<td>Number of patients</td>
<td>83</td>
<td>70</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>36 (43.4)</td>
<td>35 (50.0)</td>
</tr>
<tr>
<td>Urticaria pigmentosa, n (%)</td>
<td>36 (43.3)</td>
<td>57 (81.4)</td>
</tr>
<tr>
<td>Age at index sting (years)</td>
<td>51.3 ± 12.0</td>
<td>45.5 ± 12.9*</td>
</tr>
<tr>
<td>YJ venom-sIgE (kU/L)</td>
<td>0.62 (0.15 – 2.17)</td>
<td>0.01 (0.01 – 0.04)*</td>
</tr>
<tr>
<td>Ves v 5-sIgE (kU/L)</td>
<td>0.40 (0.08 – 1.52)</td>
<td>0.01 (0.01 – 0.02)*</td>
</tr>
<tr>
<td>Interval sting-sIgE sampling (months)</td>
<td>7.2 (3.2 – 30.8)</td>
<td>21.0 (8.1 – 103.3)*</td>
</tr>
<tr>
<td>Total IgE (kU/L)</td>
<td>20.0 (10.6 – 48.8)</td>
<td>14.4 (8.5 – 33.5)</td>
</tr>
<tr>
<td>Tryptase (µg/L)</td>
<td>24.2 (15.4 – 39.8)</td>
<td>29.7 (17.0 – 48.7)</td>
</tr>
<tr>
<td>MH (µmol/mol creatinine)</td>
<td>227 (166 – 339)</td>
<td>235 (189 – 434)</td>
</tr>
<tr>
<td>MIMA (mmol/mol creatinine)</td>
<td>2.8 (2.3 – 3.9)</td>
<td>3.6 (2.4 – 5.2)</td>
</tr>
<tr>
<td>KIT D816V mutation analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not indicated, n (%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Not performed, n (%)</td>
<td>12 (14.4)</td>
<td>16 (22.9)</td>
</tr>
<tr>
<td>KIT D816V +, n (%)</td>
<td>64 (77.2)</td>
<td>53 (75.6)</td>
</tr>
<tr>
<td>KIT D816V -, n (%)</td>
<td>8 (9.4)</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation 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 non-systemic reactors. **P < .05 between ISM systemic reactors and non-mastocytosis systemic reactors. #P < .05 between ISM non-systemic reactors and non-mastocytosis systemic reactors.

ISM, indolent systemic mastocytosis; MH, methylhistamine; MIMA, methylimidazole acetic acid; YJ; yellow jacket; Ves v 5, Vespula vulgaris antigen 5.

An overview of the severity of sting reactions is given in Table 2. 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) 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) patients. During follow-up, no fatal anaphylactic reaction occurred although two fatal anaphylactic reactions happened in our center outside the scope of this study after stopping VIT.3

Characteristics of non-mastocytosis cohort and reactions to YJ stings
Between 2009 and 2015, 313 adult patients with serum tryptase levels < 10.0 µg/L and urinary MH excretion ≤ 154 µmol/mol creatinine were diagnosed with a systemic reaction following a YJ sting. An overview of the patient characteristics is given in Table 1. These patients had higher YJ venom-sIgE levels than ISM patients with a systemic reaction...
(4.83 vs. 0.62 kU/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, non-mastocytosis patients showed higher total IgE levels (71.0 vs. 20.9 kU/L; \( P < .001 \)).

Overall, the first systemic reaction was less severe than the first reaction in ISM patients: 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.

**Table 2 | Natural course of reaction recurrence in indolent systemic mastocytosis patients.**

<table>
<thead>
<tr>
<th></th>
<th>First SR</th>
<th>First sting after first SR</th>
<th>Second sting after first SR</th>
<th>Third sting after first SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No SR (n)</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Grade I (n)</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade II (n)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade III (n)</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade IVa (n)</td>
<td>14</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Grade IVb (n)</td>
<td>58</td>
<td>26</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Total (n)</td>
<td>83</td>
<td>41</td>
<td>15</td>
<td>8</td>
</tr>
</tbody>
</table>

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 sIgE against YJ venom in ISM patients**

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

The interval between the sting and sIgE sampling affected the level of sIgE. When the interval was \( \leq 3 \) years, 79.7% (\( n = 55 \)) of ISM patients with a systemic reaction showed sIgE \( \geq 0.35 \text{kU/L} \) while levels were positive in only 21.4% (\( n = 3 \)) when the interval exceeded 3 years. In order to eliminate the time effect and approach clinical practice, the diagnostic accuracy of YJ venom-sIgE was only determined in patients in which the time interval between the sting and sIgE sampling was \( \leq 3 \) years. This cohort comprised 69 ISM patients with a systemic reaction and 43 ISM patients without a systemic reaction. In these patients, receiver operating characteristic
analysis of YJ venom-sIgE exhibited a high diagnostic accuracy in ISM patients with an AUC of 0.90 (95% confidence interval 0.84-0.96; Figure 2). The current clinical reference value of 0.35 kU\(\ell\)/L showed a sensitivity and specificity of 77.6% and 87.5%.

**Figure 2** | Receiver operating characteristic curves for sIgE against yellow jacket venom and Ves v 5 to assess the occurrence of systemic reactions in indolent systemic mastocytosis patients.

**Effect of a lower cut-off value of sIgE on diagnostic accuracy in ISM patients**
The greatest combined sensitivity and specificity was found at a cut-off value of 0.21 kU\(\ell\)/L, resulting in a sensitivity and specificity of 82.1% and 87.5%, respectively. In order to obtain an optimal sensitivity, the cut-off was lowered to 0.17 kU\(\ell\)/L, resulting in a sensitivity and specificity of 83.6% and 85.0%, respectively. Using 0.35 kU\(\ell\)/L as a reference value, positive YJ venom-sIgE levels could be detected in 79.7% (\(n = 55\)) of ISM patients with a history of a systemic reaction. Conversely, in ISM patients without systemic reactions only 11.6% (\(n = 5\)) displayed YJ venom-sIgE levels \(\geq 0.35\) kU\(\ell\)/L. Using 0.17 kU\(\ell\)/L as a reference value, positive YJ venom-sIgE levels could be detected in 84.1% (\(n = 58\)) of ISM patients with a history of a systemic reaction. Conversely, in ISM patients without systemic reactions only 14.0% (\(n = 6\)) displayed YJ venom-sIgE levels \(\geq 0.17\) kU\(\ell\)/L. In addition, in ISM patients that could not recall ever being stung by a YJ and in those that were only stung during childhood venom-sIgE levels were all \(< 0.17\) kU\(\ell\)/L (determined in 58 out of 90 patients). These results indicate that the clinical reference value of 0.35 kU\(\ell\)/L can safely be lowered to increase the sensitivity due to the infrequency of asymptomatic sensitization in ISM patients.
Diagnostic accuracy of Ves v 5-sIgE in ISM patients
In the same subgroup, receiver operating characteristic analysis of Ves v 5-sIgE showed the
greatest combined sensitivity and specificity at a cut-off value of 0.11 kU/L, resulting in
sensitivity and specificity of 80.3% and 81.5%, respectively (Figure 2). Using the > 0.11 kU/L
clinical cutoff point, additional Ves v 5-sIgE measurement correctly identified sensitization in 5
of 11 ISM patients with a systemic reaction and a YJ venom-sIgE ≤ 0.17 kUA/L, indicating a role
for Ves v 5-sIgE in diagnosing YJ venom allergy in ISM patients with negative YJ venom-sIgE
results.

Sensitization in systemically reacting non-mastocytosis patients
In non-mastocytosis patients who experienced a systemic reaction, YJ venom-sIgE levels
≥ 0.35 kU/L could be detected in 94.2% (n = 295). Sensitization to YJ venom could be
demonstrated by positive intracutaneous skin tests in all patients with a negative sIgE
outcome. In the subgroup of patients in which sIgE was measured within three years, the
positive sIgE rate was only slightly higher than in in overall group (94.8%, n = 272). In contrast
to ISM patients, 87.5% showed sIgE levels above the threshold of 0.35 kU/L when the interval
exceeded three 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 an ISM patient 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% (82/243) versus 3.0%5), but are also far
more often very severe at the first systemic reaction (69.9% versus 22.0%) and have a higher
recurrence rate when not treated by VIT (97.5% versus 50%21).

The high prevalence of YJ venom allergy in ISM patients is probably a slight overestimation
because other ISM patients with subtle or absent symptoms of ISM may easily be missed.22
Nevertheless, the prevalence of yellow jacket induced anaphylaxis is strikingly higher than
that found in the general population, but similar to that previously reported in ISM patients
(25.0%).23 In addition, we showed that once stung, the risk rises to 54.0% (83/153). Sensitization
without a history of clinical reactions is found in 18.8-38.1% of the general population and
poses a risk of a future systemic reaction in only 5.3-17.0%.24-29 We found that asymptomatic
sensitization is rare in ISM patients and occurs in only 8.6-13.0%, depending on the cut-off point. Conversely, symptomatic sensation occurred in 34.2% of ISM patients, 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 if an auto-epinephrine injector would have sufficed in light of the rapid and dramatic course of the reaction. Would prophylactic VIT haven been an option? Although our findings suggest that sensitization is more strongly associated with systemic reactions in ISM patients, the consequences on future reaction risk remains uncertain because prospective analysis is hard to achieve due to the rarity of the disease, the infrequent occurrence of YJ stings and the strong contra-indication against diagnostic sting challenges in ISM patients.

Next to significantly more severe reactions and re-systemic reactions, the baseline frequency of systemic reactions in stung ISM patients is about 50% and comparable to the risk of re-systemic reactions for current non-mastocytosis VIT eligible patients, which supports the notion that these patients should be eligible for treatment.\textsuperscript{30} We feel that preventive treatment should be discussed with all ISM patients 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 ISM patients that 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 3.75-7.5 years, depending on the patient’s occupation.\textsuperscript{31}

Pivotal for these recommendations is the use of an optimal clinical reference value for YJ venom sIgE. ISM patients 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 dataset of adult ISM patients. Only one other study has evaluated the current threshold of 0.35 kU/L in patients with mast cell disorders and advised to lower the reference value to 0.10 kU/L.\textsuperscript{32} In that study including 17 systemic mastocytosis patients 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 \( \geq 0.35 \) kU/L and could be elevated to 91.8% using a cut-off of 0.10 kU/L. However, the specificity was not taken into account. Applying the same threshold of 0.10 kU/L in our ISM patients, we find 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 cut-off of 0.21 kU/L (82.1% and 87.5%, respectively). However, because missing the diagnosis of YJ venom allergy could have serious consequences, a lower cut-off of 0.17 kU/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/L. Remarkably, the diagnostic accuracy at 0.17 kU/L equals the diagnostic accuracy of sIgE reported in patients without ISM. Of note, the time interval between the sting and sIgE sampling seems more important to the level of sIgE in ISM patients than in non-mastocytosis patients, because only a minority of ISM patients show positive sIgE levels after three years while the majority of non-mastocytosis patients 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.

The diagnostic accuracy of Ves v 5-sIgE was lower than that of YJ venom-sIgE in ISM patients. In agreement with a previous report demonstrating improved sensitivity when adding Ves v 5-sIgE, Ves v 5-sIgE improves the diagnostic accuracy of YJ venom-sIgE when these are combined in patients with YJ venom sIgE levels ≤ 0.17 kU/L. 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 ≤ 0.17 kU/L.

In conclusion, the high diagnostic accuracy of YJ venom-sIgE in ISM patients 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 ISM patients 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/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 ≤ 0.17 kU/L. Finally, based on the relatively low rate of asymptomatic sensitization and the high prevalence of severe systemic reactions in ISM patients we recommend discussing the possibility of VIT with all ISM patients exhibiting elevated YJ venom sIgE, even if they are hitherto asymptomatic, in order to arrive at an optimal individualized management strategy.

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REFERENCES