Usefulness of Omalizumab and Sting Challenge Test in Hymenoptera Venom Allergy and Mastocytosis

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A clear relationship has been demonstrated between hymenoptera venom anaphylaxis (HVA) and systemic mastocytosis (SM). In fact, up to 26% of the patients with a life-threatening reaction after the sting of bees and/or wasps might present clonal mast cells (MCs) [1]. Venom immunotherapy (VIT) has proved to be effective in SM patients who have an IgE-mediated reaction, although there is a higher risk of adverse reactions regarding general population, especially in the build-up doses and, thus, omalizumab may be of use while reaching maintenance [2]. VIT is effective in the majority of patients treated and in around 75% of patients with SM [2], but no in vitro techniques are able to predict the effectiveness of treatment in a specific patient [3]. Sting challenge test (SCT) has proven to be the most reliable method and gold standard to monitor the effectiveness of the treatment [4], nevertheless its use in patients at higher risk of reactions such as clonal MC patients is controversial.

A 32-year-old-man, beekeeper as a hobby, was stung by 8 honeybees in the summer of 2015 and immediately experienced bad general condition, dizziness without loss of consciousness and chest tightness. Intradermal skin test was positive with *apis mellifera* extract at 0.1 mcg/ml, and negative with *vespula* species and *polistes dominula* until a
concentration of 1 mcg/ml (ALK Allergologisk Laboratorium A/S). Specific IgE (sIgE) determinations (ImmunoCAP Thermo Fisher and Immulite 2000, Siemens Diagnostics) were carried out and showed positive results (Figure 1). VIT was initiated without premedication (Pharmalgen® *apis mellifera*, ALK) and a maintenance dose of 100 mcg was reached in 3 weeks with no incidence. After the seventh monthly maintenance dose (which belonged to the same batch than previous doses), the patient experienced within minutes chest tightness, dizziness and a rapid drop in blood pressure down to 60/40 mmHg. He was pre-medicated with 50 mg of oral prednisone and 10 mg of loratadine for the next month dose and the 100 mcg were split between the two arms, but he presented the same reaction as in the previous month. A MC disease was then suspected. VIT was interrupted and a bone marrow (BM) study was performed to evaluate all the disease characteristics used for the diagnosis of SM, such as BM MC cytology, histology and immunochemistry, flow cytometry immunophenotyping using specific gating strategies for the detection of BM MCs present at low frequencies, and the study of *KIT* mutation in purified MCs [5]. A final diagnosis of indolent systemic mastocytosis without skin involvement (ISMs-) was reached, and the patient started with disodium cromolyn daily as part of the recommended treatment for this disease. In order to resume immunotherapy, he began with 300 mg of omalizumab every 4 weeks and, after two doses, VIT was restarted without additional premedication and with good tolerance. Monoclonal antibody was upheld for a year – a little longer than the time elapsed in previous reaction with VIT - and before discontinuation a basophil activation test (BAT) was carried out, with negative result (Figure 1). Most patients with mastocytosis are protected by VIT, but minority may develop systemic adverse reactions (SAR) after re-exposure. In this
situation it is recommended to increase the maintenance dose to 200 mg or more, since the magnitude of therapeutic success correlates with venom dose [6]. Besides, Api m 2 seemed to be the culprit allergen in the present case, and it has been considered as risk factor of SAR [7]. The patient had not been field re-stung since the beginning of VIT so when we confirmed the decrease in sIgE values once the effect of omalizumab disappeared – 9 months, according to the manufacturer -, a SCT was performed according to the proposed methodology [4] without prompting any reaction.

Although the present work is based only one case report, several relevant conclusions arise from the results. Patients presenting with anaphylaxis during hymenoptera stings are at high risk for clonal mast cell disorders [1]. Along with the determination of baseline serum tryptase in patients with anaphylaxis following hymenoptera stings, the clinical features of the anaphylaxis should be also taken into account since there is an association between the presence of cardiovascular symptoms in the absence of both urticaria and angioedema and ISMs- and clonal mast cell activation syndromes (MCAS) [8]. Furthermore, in ISMs-, MCs represent only a very small proportion of all nucleated BM cells and serum baseline tryptase levels are usually under reference values (<11.4 μg/L).

The diagnosis of MC diseases requires the performance of a BM biopsy, which is an expensive, sensitive and invasive procedure. It is, therefore, important to define criteria to select patients with HVA who should undergo this procedure [5]. In this context, the application of screening tools that help in predicting clonality with high sensitivity and specificity, such as the REMA Score, are useful [8]. Another relevant issue is the usefulness of component resolved diagnosis (CRD) (native or recombinant) to easily identify the allergen responsible of a reaction, especially when the culprit allergen might
be associated with higher rate of SAR or might be under-represented in the commercial diagnostic or therapeutical extracts. Moreover, omalizumab has demonstrated its utility, as occasionally described [2], as VIT adjuvant in patients with clonal MCs who were unable to tolerate immunotherapy. The potential role of disodium cromolyn also as VIT adjuvant remains unknown, but cannot be excluded. Finally, performing SCT in patients with mastocytosis is a controversial topic since systemic reactions after its performance have been observed in higher rates regarding general population (23.9% vs. 9.3%) [9].

CRD results in a more accurate knowledge of the patient’s sensitization profile, which might help decreasing that rate. Nevertheless, this assumption needs further assessment. SCT has shown the highest correlation to evaluate the effectiveness of VIT and in improving health-related quality of life [4], and patients who react to a sting challenge while receiving conventional VIT are protected by an increased maintenance dose [10]. Mastocytosis are known to be closely related to HVA [2], patients are more likely to present adverse reactions during VIT, they are at greater risk of recurrence once treatment is discontinued and, henceforth, experts recommend that they should receive lifetime VIT [3, 4]. For all these reasons, being extremely cautious, it would be appropriate to keep in mind the possibility of performing SCT, if needed, in a patient with clonal MCs and an accurate molecular sensitization diagnosis.

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References


**Figure 1.** Chronological summary of the study and allergic work-up carried out.

<table>
<thead>
<tr>
<th>Total IgE (IU/L)</th>
<th>73</th>
<th>69</th>
<th>297</th>
<th>54.9</th>
</tr>
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<tbody>
<tr>
<td>sIgE apis (IU/L)</td>
<td>5.82</td>
<td>0.25</td>
<td>NA</td>
<td>1.96</td>
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<tr>
<td>sIgE (Apilim 1/NApilim 1 (IU/L))</td>
<td>NA/NA</td>
<td>NA/1.22</td>
<td>0.05/3.78</td>
<td>0.05/NA</td>
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<tr>
<td>sIgE (Apilim 2/NApilim 2 (IU/L))</td>
<td>NA/NA</td>
<td>1.54/26.6</td>
<td>7.75/212.29</td>
<td>0.66/NA</td>
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<tr>
<td>sIgE (Apilim 3/NApilim 3 (IU/L))</td>
<td>NA/NA</td>
<td>0.03/NA</td>
<td>0.76/NA</td>
<td>0.03/NA</td>
</tr>
<tr>
<td>sIgE (Apilim 4/NApilim 4 (IU/L))</td>
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<td>NA/0.4</td>
<td>NA/0.31</td>
<td>NA/NA</td>
</tr>
<tr>
<td>sIgE (Apilim 10/NApilim 10 (IU/L))</td>
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<td>NA/0.75</td>
<td>NA/NA</td>
<td>NA/NA</td>
</tr>
<tr>
<td>sIgE polistes (IU/L)</td>
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<td>-0.1</td>
<td>NA</td>
<td>0.25/NA</td>
</tr>
<tr>
<td>sIgE polistes (IU/L)</td>
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<td>NA</td>
<td>1.56/NA</td>
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<td>NA</td>
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<td>0</td>
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<td>sIgE IgE (Apilim 2 (IU/L))</td>
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<td>0.17</td>
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<td>Baseline tryptase (ng/mL)</td>
<td>8.2</td>
<td>8.15</td>
<td>8.75</td>
<td>8.55</td>
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<td>Bone marrow study</td>
<td>ISM-</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-sting challenge</td>
<td></td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BAT, basophil activation test; BM, bone marrow; CCD, Cross-reacting carbohydrate determinants; ISMs-, indolent, systemic mastocytosis without skin lesions; n, native; NA, not available; r, recombinant; sIgE, specific immunoglobulin E; VIT, venom immunotherapy.