Anaphylaxis after Hymenoptera sting without detectable specific IgE

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SUMMARY

Current guidelines for venom immunotherapy suggest that immunotherapy should be performed only in patients with IgE mediated systemic reactions. However, opinions on the diagnosis and treatment of patients with systemic reactions in the absence of IgE are quite varied. We present a patient with a history of atypical systemic reactions after a bee sting. Skin tests and specific IgE for bee venom were negative. We performed a sting provocation test in order to characterize the nature and mechanism of reaction. The provocation test was positive and mast cell activation was proved by tryptase elevation. We decided to treat the patient with immunotherapy. After beginning immunotherapy we were able to detect specific IgE for bee venom in the serum.

KEY WORDS

anaphylaxis, Hymenoptera, negative specific IgE

Case report

A 66-year-old man was referred because of a suspected allergy to bee venom. He had experienced a bee sting in the neck 3 months prior to referral. A few minutes after being stung, he took antihistamines and methylprednisolone. About 15 minutes after the sting he felt tingling in the ears, paresthesia of the lips, and shortness of breath, and then he fainted. He was transferred to the emergency unit, where he was found to have low blood pressure and treatment with adrenalin was started. The patient did not notice any flushing, pruritus, urticaria, or angioedema. He had experienced a similar reaction after a bee sting 2 years earlier.

Skin prick tests with bee and wasp venom (Venomenhal, HAL, Haarlem, the Netherlands) in concentrations up to 100 μg/L and an intradermal test with 0.1 μg/L were negative. There was no delayed reaction to the skin tests. Specific IgE in serum (UniCAP, Pharmacia, Uppsala, Sweden) was below 0.35 μg/L. Total serum tryptase level (UniCAP, Pharmacia, Uppsala, Sweden) was 4.79 μg/L (normal < 10 mg/L). We repeated the skin tests and specific IgE measurements after 6 weeks and the results were negative again (Table 1).

After receiving informed consent, we performed the sting provocation test in the intensive care unit with a live bee. The patient felt pain at the sting site, while the stinger remained in the skin, but no wheal-and-flare reaction developed. Approximately 10 minutes later the patient reported paresthesia and itching of the lips, tin-

gling and pressure in the head, chest pain, and dyspnea. His respiratory rate rose from 16 to 32/min and his heart rate was 80/min. Blood gas analysis revealed hyperventilation (pH 7.502, pCO2 3.84 kPa, pO2 9.27 kPa). Fifteen minutes after the sting, his blood pressure suddenly dropped to its lowest value of 65/30 mmHg and an idioventricular rhythm appeared on the ECG monitor with some episodes of non-sustained ventricular tachycardia. The patient experienced no skin symptoms and he recovered completely within 20 minutes of treatment. His serum tryptase 20 minutes after the beginning of the reaction was 33.7 μg/L (Table 1).

On the next day we introduced venom immunotherapy (VIT). During the rush phase with a dose of 0.2μg of bee venom the patient experienced a mild systemic reaction. During further immunotherapy there was no reaction. The specific IgE for bee venom was 0.52μg/L after the rush phase of immunotherapy (Table 1).

Table 1. Serum specific IgE levels and tryptase level in μg/L.

	sIgE bee	sIgE wasp	tryptase
First visit	< 0.35	< 0.35	4.28
Second visit	< 0.35	< 0.35	4.79
Provocation	< 0.35	< 0.35	33.70
After rush phase	0.52	< 0.35	4.19

Discussion

Anaphylaxis after a Hymenoptera sting is a potentially fatal condition, but it can be successfully prevented with VIT. Current guidelines recommend that immunotherapy should be started only when the presence of specific IgE is proven with skin tests or found in the serum. Some authors give the endpoint titration for intradermal skin test as 10^{-3} g/l (1μg/ml) and others as 10^{-4} g/l (0.1 μg/ml); in prick tests, it ranges from 10^{-1} g/l (100 μg/ml) to 1 g/l (1). There is no consistent recommendation concerning the treatment of patients with a history of severe systemic reaction and negative allergy workup. Allergists' opinions differ. Some allergists have proposed having every patient with a history of Hymenoptera sting allergy undergo a provocation test (2). Others believe that provocation test can only be used for patients treated with VIT for assessing the efficacy of treatment (3). On the other hand, many argue that the provocation test should never be performed as a diagnostic procedure (1).

Golden et al. showed that 2 of 14 volunteers with positive history, negative skin test response, and negative venom-specific IgE experienced systemic reactions after the sting challenge. They describe a subset of patients with a distinct clinical pattern, "vascular anaphylaxis," with abrupt onset of severe hypotension without cutaneous or respiratory symptoms (4).

A negative skin test and absence of specific IgE may indicate a non-allergic reaction, such as anxiety or panic, conditioned reflex reactions, or toxic reactions; or the limited diagnostic sensitivity of the currently available tests for routine diagnostic workup. Another possible explanation is a loss of sensitivity when the period between reaction and testing is very long, although some patients with negative tests report a recent severe systemic reaction. On the other hand, in the days or weeks after a sting reaction, a skin test can be negative because of a refractory period of anergy (5). Occult mastocytosis can be a reason for anaphylaxis after Hymenoptera sting in patients without demonstrable IgE (6). A non-IgE mechanism, such as that responsible for contrast media reactions, is also possible. Some reactions have occurred with the first known sting exposure (7).

New *in vitro* cellular tests are also available for the diagnosis of Hymenoptera venom allergy, but they are not recommended for routine clinical practice (8).

In our patient, the history and clinical manifestations were not completely typical for anaphylaxis because there were no skin symptoms such as flushing, urticaria, pruritus, or angioedema. Systemic mastocytosis was excluded with the low level of total serum tryptase. The history indicated possible hyperventilation syndrome. Emergency treatment for hyperventilation is quite different from emergency treatment of allergic reactions. We believe that application of adrenaline to an older patient with possible latent cardiovascular disease could also be life threatening, especially if it is given unnecessarily, such as because of hyperventilation. We decided to perform the provocation test in the intensive care unit, and this is how we excluded hyperventilation as the sole reason for systemic reaction.

Considering the intensity of the reaction, which was mediated by mast cell activation, we decided to treat the patient with VIT.

It was an interesting finding that, after the introductory phase of venom immunotherapy, we were able to detect specific IgE for bee venom, but the skin prick test and intradermal test remained negative. Specific IgE usually increases transiently at the beginning of immunotherapy and the provocation test might also act as a booster for IgE level (9, 10). Both factors may have contributed to the increased level of IgE in our patient.

REFERENCES

1. Mueller U, Mosbech H. Immunotherapy with Hymenoptera venoms. Position paper. Allergy. 1993;14 (Suppl 48):37–46.

2. Blaauw PJ, Smithuis LOMJ. Evaluation of the common diagnostic methods of hypersensitivity for bee and yellow jacket venom by means of an in-hospital insect sting. J Allergy Clin Immunol. 1985;75:556–62.

3. Müller U, Helbling A, Berchtold E. Immunotherapy with honeybee venom and yellow jacket venom is different regarding efficacy and safety. J Allergy Clin Immunol. 1992;89:529–35.

4. Golden DBK, Sobotka AK, Norman PS. Insect sting allergy with negative venom skin test responses. J Allergy Clin Immunol. 2001;107:897–901.

5. Golden DBK, Tracy JM, Freeman TM, Hoffman DR. Negative venom skin results in patients with histories of systemic reaction to a sting. J Allergy Clin Immunol. 2003;112:495–8.

6. Ludolph-Hauser D, Ruëff F, Fries C, et al. Constitutively raised serum concentration of mast cell tryptase and severe anaphylactic reactions to Hymenoptera stings. Lancet. 2001;3557:361–2.

7. Reisman RE. Insect sting allergy: The dilemma of the negative sting test reactor. J Allergy Clin Immunol. 2001;107:781–2.

8. Eberline-König B, Ring J. Diagnosis of IgE-mediated hymenoptera venom anaphylaxis in the patients with negative skin tests and negative RAST using cellular in vitro tests. J Allergy Clin Immunol. 2004;113:1223; authors' reply 1223–4.

9. Golden DBK, Addison BI, Kwiterovich KA, et al. Natural history of Hymenoptera venom allergy (HVA) in adults. J Allergy Clin Immunol. 1992;89:291.

10. Košnik M. Anaphylaxis to venom without IgE antibody. Allergy. 2000;55:676–7.

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