
Case report of venom immunotherapy for a patient with large local reactions

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Background: Inadvertent Hymenoptera stings reportedly elicit large local reactions in up to 17% of the general population. Current practice parameters do not recommend venom immunotherapy (IT) for these cases.

Objective: The goal of this case study was to investigate the clinical and immunologic consequences of venom IT in a newly sensitized individual with large local reactions using an intentional sting challenge before and after treatment to document changes in reaction severity.

Methods: A 47-year-old man became honeybee venom (HBV)-allergic with progressively larger reactions at honeybee sting sites with subsequent stings. Then, a sting on his forefinger produced a large (62 cm) local reaction with swelling throughout the arm that persisted for more than 4 weeks with severe pain. He refused steroid therapy and voluntarily requested venom IT with honeybee-sting challenges to monitor clinical parameters and immunologic changes in his skin and serum before and 7 months post-HBV maintenance IT.

Results: A single pre-IT bee sting challenge produced an 11.4-cm wheal with 13-cm erythema at the sting site after 15 minutes, followed by several weeks of edema that involved the entire arm. After rapid escalation of venom IT to maintenance in 7 weeks, a post-maintenance IT sting challenge with two honeybees produced a 3-cm diameter erythema with no wheal at 15 minutes and no late-phase induration. Complete loss of any visible reaction at the field sting site resulted after 13 months of maintenance venom IT. A HBV-specific IgG antibody level >3.5 $\mu\text{g/mL}$ and IgG/IgE antibody molar ratio >500 persisted over the period of venom IT, with venom skin reactivity diminishing 100-fold.

Conclusions: These results support venom IT use in the treatment of Hymenoptera venom-sensitive individuals who experience large local reactions and are at risk for repetitive inadvertent stings.

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INTRODUCTION

Large local reactions after Hymenoptera stings occur in a reported 7% to 17% of the general population, with a frequency two to three times that of systemic reactions.^{1–3} Most large local reactions result from an IgE-mediated mechanism, because 50% to 80% of these individuals are skin test-positive

to one or more Hymenoptera venoms. Although the incidence of systemic reactions is 5% to 10% among individuals experiencing large local reactions, most are mild and only 1% to 2% are considered life-threatening. For this reason, large local reactors are not currently viewed as candidates for venom immunotherapy (IT) under practice guidelines,^{3,4} and only medication and avoidance are prescribed.

This report presents a nonatopic man who, after 2 years of experiencing progressively larger local reactions to honeybee field stings (FSs), requested honeybee venom (HBV) IT and a pre- and postvenom IT sting challenge to document treatment efficacy. The sting

challenge outcome and immunologic results demonstrate the clear benefit of venom IT in this large local reactor.

CASE REPORT

In spring 1996, a 47-year-old male moved into a home next to a farm with honeybee hives. The year before, he had participated as a nonatopic control subject in research at the Johns Hopkins Asthma and Allergy Center where he had a negative allergy history, negative multiallergen screen (Phadiatop, Pharmacia, Peapack, NJ) and negative puncture skin tests (extracts from Greer Laboratories, Lenoir, NC) and IgE antibody serology (CAP System, Pharmacia) to 30 common aeroallergens, venoms (including HBV), and foods. During 1996 and 1997, he experienced four and six honeybee field stings, respectively (FS $\times 10$; Fig 1), with progressively larger reactions at the sting sites. In May 1998, a FS on his forefinger produced a large local reaction involving swelling that extended 62 cm from his finger to his axilla (Fig 1). The swelling persisted for >4 weeks with severe pain. During this period, he refused all forms of medical treatment recommended by his allergist, including steroids. His HBV-specific IgE antibody converted from negative to positive in May 1998 as evaluated by both intradermal HBV skin test (positive at 0.01 mg/mL) and radioallergosorbent test (13 ng/mL; Fig 1). He practiced careful avoidance until March 1999, when he requested venom IT as a result of fear about a future systemic reaction. Immediately before starting venom IT and after 5 months after reaching maintenance IT, he volunteered with informed consent to a honeybee-sting challenge (SC, Fig 1) as previously described⁵ to docu-

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ment the efficacy of his venom IT program.

METHODS

Monitored clinical and immunologic parameters included: 1) the magnitude of observed honeybee sting-induced reactions in terms of the absence (0) or presence (+) of reactions and the magnitude of the swelling when it was present; 2) intradermal skin test (ID-ST) titer (concentration of HBV required to produce at least a 5 mm wheal and 20 mm erythema); 3) IgE anti-HBV in ng/mL; 4) IgG anti-HBV in $\mu\text{g/mL}$; and 5) the IgG anti-HBV/IgE anti-HBV molar ratio for various time intervals from 30 months before to 15 months after HB venom IT initiation. IgE and IgG anti-Hymenoptera venom were measured at the Johns Hopkins Dermatology, Allergy, and Clinical Immunology Reference Laboratory with previously described methods.⁶ The IgG/IgE molar ratio was computed as the concentration of IgG anti-HBV in ng/mL divided by the concentration of IgE anti-HBV in ng/mL in the serum. Venom ID-STs and IT⁴ (Fig 1) were performed using commercial ALK-Abello (Horsholm, Denmark) venom extracts as recommended in the product package insert, except that the maintenance IT dose of 100 μg of HBV was achieved after seven weekly treatments.

RESULTS

Figure 1 summarizes the clinical (honeybee sting reaction and event line) and skin- and serum-based immunologic measures before and after SC and venom IT. At the time of initial honeybee stings in 1996, there was no clinical or immunologic evidence of sensitization in the subject, and the stings produced transient pain with no abnormal reaction. By May 1998, a honeybee sting on his finger caused a painful large local reaction of 62 cm in length and both intradermal skin tests and serology performed immediately thereafter confirmed the presence of IgE antibody specific to HBV. The pre-IT sting challenge on March 4,

1999 with a single honeybee sting on the forearm produced an 11.4-cm wheal with 13-cm erythema at the sting site by 15 minutes. The next day, swelling had grown in size to involve the entire arm. One week later, HBV IT was initiated with rapid escalation to maintenance in 7 weeks with no apparent systemic reactions. After 5 months of maintenance IT, his post-maintenance SC with 2 honeybee stings produced a milder local reaction with 3-cm diameter erythema (no wheal) at 15 minutes and no observed late-phase induration. He has contin-

ued on HBV IT for >15 months with complete ablation of local reactions after his monthly IT injection and, most importantly, an absence of reactions to occasional honeybee FSs (eg, June 2000 on Fig 1). The IgG anti-HBV remained above the 3 $\mu\text{g/mL}$ target,⁷ whereas his IgE anti-HBV ranged from 4 to 5 ng/mL during the observation period while on maintenance IT.

DISCUSSION

Current practice parameters preclude Hymenoptera venom-sensitized individuals who experience large local re-

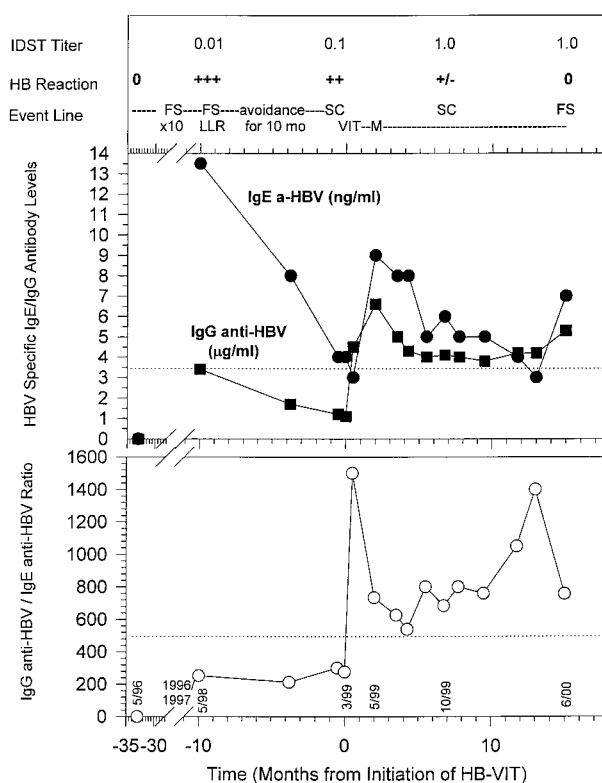


Figure 1. Changes in the HBV intradermal skin test (ID-ST) titer (HBV concentration producing at least a 5 mm wheal and 20 mm erythema), localized honeybee sting reactions and clinical event timeline, large local reactions (LLRs), field stings (FSs), sting challenges (SCs), initial and maintenance (M) venom IT indicated (*top panel*), IgE and IgG anti-HBV levels in serum (*middle panel*), and IgG to IgE anti-HBV molar ratio (*bottom panel*) in a 47-year-old male from the time he moved to the country (–33 months) to 15 months post-IT initiation. Inadvertent honeybee sting induced skin reactions ranged from no reaction (0 at –33 and +15 months) to swelling that crossed 2 or 3 joints (2+ or 3+, respectively). A ± sting reaction indicates that there was a mild localized wheal and erythema at the sting site. The intradermal skin test titer ranged from 0.01 to 1.0 $\mu\text{g/mL}$. The HBV-specific IgE (closed circles, ng/mL) and HBV-specific IgG (closed squares, $\mu\text{g/mL}$) are reported with levels of IgG anti-HBV >3 $\mu\text{g/mL}$ as indicated by the dotted line (*middle panel*). The *bottom panel* presents the IgG to IgE antibody molar ratio observed in the serum. Molar IgG/IgE antibody ratios >500 were observed only after venom IT. No data are available to indicate that an IgG/IgE ratio of 500 or greater identifies a protected from a nonprotected bee-sensitive individual because those clinical challenge studies have not yet been performed.

actions from receiving venom IT, because only 5% to 10% of these individuals reportedly progress to experience systemic reactions, and most are not life-threatening.⁸⁻¹⁰ Large local symptoms are therefore managed with a brief course of high-dose steroids. Steroid administration, however, does not reduce the risk for systemic reactions. The subject in the present case refused standard medical therapy involving steroids for fear of a systemic reaction. He opted instead to receive venom IT that could reduce his risk for systemic reactions with subsequent stings. Although IT may not be a suitable treatment for all large local reactors, patients with more frequent and progressively more severe large local reactions have increased risk if they are prescribed only steroids, and therefore, they may receive greater relative benefit from venom IT. The progressively increasing severity of his large local reactions, the high repeat sting frequency because of his living near bee hives, and his fear of systemic reactions and the morbidity associated with the large local reaction led him to request venom IT. The SC and immunologic testing confirmed a decline in skin sensitivity that was concomitant with a reduction in clinical symptoms. The absence of previously experienced large local reactions with an FS after IT was considered an enhancement to the man's quality of life.

The literature is unclear on whether venom IT reduces large local reactions in venom-allergic adults. Mauriello et al⁹ reported that venom allergic patients with large local reactions experience the same frequency and severity of large local reactions regardless of whether or not they have received venom IT. In contrast, Light et al¹¹ reported that large local reactions in adult beekeepers decrease in size with increased venom exposure through repetitive stings. Schuberth et al¹² studied 124 children with cutaneous systemic reactions after Hymenoptera stings, and they observed that the frequency of subsequent large local reactions to stings was significantly lower in the group receiving IT than in the

untreated group (5% vs 33%, respectively). The results of this single report support the conclusion that venom IT can essentially eliminate localized skin reactions in honeybee-allergic individuals.

This case report that involves sensitivity to HBV does not allow us to generalize the results to other medically important Hymenoptera venoms. The clinical and immune responses are reportedly different in individuals who become sensitized to honeybee and vespid venoms,¹³ and they vary with the frequency of stings. Beekeepers, for instance, often develop allergic reactions if they are stung infrequently (<25 times per year). However, they may immunize themselves if they are stung more often (>100 times per year).¹⁴ Further, whereas the IgE and IgG antibody responses do not always correlate with the reaction severity or frequency, the HBV-specific IgG antibody level in this case remained >3 µg/mL while on maintenance IT which, in at least one study, has been associated with reduce risk for systemic reactions.⁷

CONCLUSION

In the case of an allergy to Hymenoptera venom, current practice parameters are designed to reduce mortality associated with life-threatening sting reactions. In contrast, it is widely accepted that IT for allergies to pollens, fungal spores, pet epidermal, and dust mite allergens is performed primarily to reduce morbidity. As such, reconsideration of the goals of venom IT expressed in the practice parameters for Hymenoptera venom allergies may be warranted. This could be especially important for individuals who fear that subsequent stings may elicit systemic reactions because they work or play in locations where they experience frequent inadvertent stings. Revised guidelines might endorse the concept that reduction of morbidity and improved quality of life may justify venom IT for large local reactors, especially in patients with particularly severe reactions or frequent exposures. The indications for venom IT would

still require positive venom skin tests or serum IgE antibodies, but the therapeutic decision could be made largely on clinical grounds.

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