

Brief communications

Rush Hymenoptera venom immunotherapy: Successful treatment in a patient with systemic mast cell disease

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Systemic mast cell disease (SMCD) represents an uncommon group of clinical disorders, ranging from the primarily cutaneous manifestations of urticaria pigmentosa to the malignant proliferation of mast cells or mass cell leukemia.¹⁻³ SMCD is associated with an increase in mast cell numbers, even in its more benign forms, and may manifest with recurrent episodes of severe anaphylaxis including profound hypotension.⁴ In the context of a classic IgE-mediated allergic reaction, patients with mastocytosis may experience more severe symptoms because of increased mast cell numbers and secondary mediator release.⁴ The disease has also been characterized as one of increased mast cell activation with chronically elevated mediators.^{5, 6} The reported experience with immunotherapy in patients with this disorder is somewhat limited, particularly with regard to Hymenoptera venom anaphylaxis.

CASE REPORT

We would like to report our experience with L. D., a 43-year-old man in the U.S. Army who was first seen with a history of mastocytosis and recent insect sting anaphylaxis. The patient recalled numerous insect stings from presumed honeybees and yellow jackets with only local reactions during the 1980s. The exact dates of these stings were not available from the patient. In 1991, he was stung by an unidentified flying insect and experienced rapid onset of hypotension, requiring emergency resuscitation with epinephrine, intravenously administered fluids, and corticosteroids despite ongoing maintenance therapy with hydroxyzine and ranitidine. He responded to this emergent treatment with no further complications.

Abbreviation used

SMCD: Systemic mast cell disease

The patient was in generally good health until 1975 when pruritic skin lesions developed. A skin biopsy of a pigmented macular lesion confirmed the classic findings of urticaria pigmentosa. By 1983, spontaneous anaphylaxis with malaise, abdominal pains, and recurrent hypotension had also developed. Subsequent evaluations confirmed the diagnosis of indolent mastocytosis with localized areas of increased uptake on bone scan but no anemia or thrombocytopenia. L. D. received long-term H₁ and H₂ antagonist therapy, which attenuated the severity and frequency of the attacks.

The decision to proceed with venom immunotherapy was made after considering the severity of the patient's reaction, his lifestyle (favoring outdoor activities), a history of numerous prior stings, and his active duty military status. Because the patient could not tolerate the cessation of antihistamine therapy, demonstration of the presence of increased levels of venom-specific IgE was confirmed by RAST by the Johns Hopkins School of Medicine Dermatology, Allergy and Clinical Immunology Laboratory. Wasp, yellow hornet, and white-faced hornet venom-specific IgE levels were less than 1 ng/ml (negative serologic assay result for this laboratory). The levels of honeybee and yellow jacket venom-specific IgE were both 9 ng/ml. Venom-specific IgG was also detected before venom immunotherapy at 1.9 (for honeybee) and 1.2 µg/ml (for yellow jacket).

Although slower schedules of venom immunotherapy are widely used, some patients benefit from an accelerated or "rush" protocol. With this patient's background mast cell disorder, local sources were unwilling to provide routine immunotherapy, and he resided 3 hours from our treatment area at Walter Reed Army Medical Center. Additionally, the patient was considering a move within 6 to 12 months. A slow, weekly schedule of venom immunotherapy would present a potential risk of prolonged periods of increased IgE and weekly anaphylaxis. In the event that corticosteroid prophylaxis was added, a prolonged period of prednisone use with its own attendant side effect potential could be expected. With informed consent, the patient selected a rush venom immunotherapy program.⁷⁻¹⁰

Table I summarizes the cumulative doses of each venom given to the patient by day of therapy. L. D. was

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The opinions and assertions expressed in this article do not reflect the official position of the Department of the Army or the Department of Defense.

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J ALLERGY CLIN IMMUNOL 1994;94:556-9

1/54/56339

TABLE 1. Cumulative daily doses of rush honeybee and yellow jacket venom

Day	HB	YJ
1	0.0011	0.0011
2	0.121	0.121
3	7.1	7.1
4	5.0*	35
5		100
10	6.5	100
11	24	
12	140	
19	50	50
33	60	50
47	80	60
54	100	80†
68	100	100
79	100	100
107	100	100
139	100	100
170	100	100
207	100	100
243	100	100
338	100	100

Prednisone (50 mg/day) was given as prophylaxis.

HB, Honeybee; YJ, yellow jacket.

*Systemic reaction, mild.

†All corticosteroids withdrawn.

admitted to the hospital for a 5-day period, pretreated with prednisone (50 mg administered orally starting 18 hours before the first shot at 6-hour intervals, then every morning of the first 5 days of therapy). Administration of hydroxyzine and ranitidine was continued with the addition of astemizole prophylaxis. A heparin lock was placed, and routine cardiovascular monitoring was performed throughout the procedure. Starting at 0.05 ml of 0.001 μ g/ml of honeybee and yellow jacket venom, each dose was given at 30-minute intervals. Both venoms were given on days 1 through 5, but a single injection was given at any one time. Except for mild local soreness, L.D. experienced no systemic effects until day 4 when he noted mild subjective throat tightness, generalized malaise, and some nausea. He was treated with one injection of epinephrine, which promptly resolved the symptoms. Because a local wheal and flare reaction was only evident at the honeybee injection site, administration of this venom was briefly interrupted until day 10. The yellow jacket venom dosage was decreased by 50%, and then therapy was continued at 30-minute intervals to achieve a cumulative dose of 100 μ g on day 5. Honeybee venom immunotherapy was continued on day 10 by a modified rush schedule to achieve a cumulative dose of 140 μ g on day 12. The patient's maintenance dose of prednisone was tapered by day 10, but delayed onset of generalized arthralgias and myalgias was noted a few hours after each subsequent shot session. There was no evidence of proteinuria, increased erythrocyte sedimentation rate

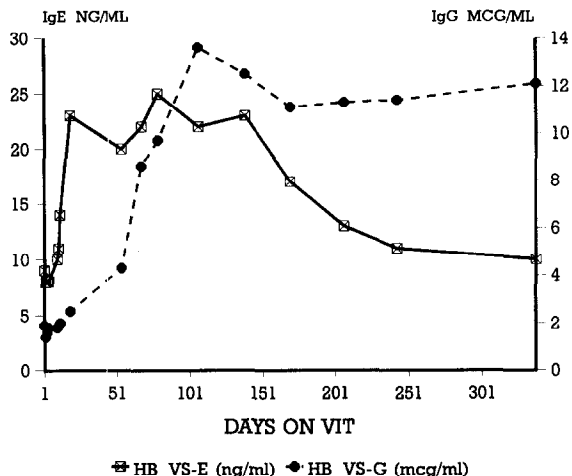


FIG. 1. Honeybee venom immunotherapy: venom-specific IgE (VS-E) and venom-specific IgG (VS-G) levels during immunotherapy.

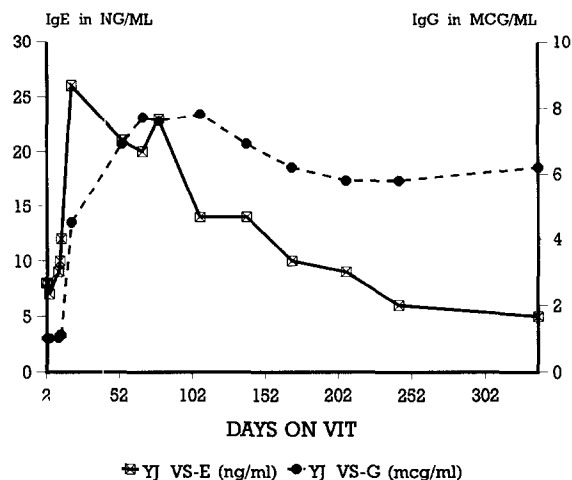


FIG. 2. Yellow jacket venom immunotherapy: venom-specific IgE (VS-E) and venom-specific IgG (VS-G) levels during immunotherapy.

(Westergren method), or other hematologic or hepatic abnormalities. A single dose of prednisone on the morning of the now weekly shots was restarted until day 54; at this point all postinjection symptoms cleared.

Fig. 1 shows the levels of honeybee venom-specific IgE and IgG. The patient's injection-related rise in venom-specific IgG occurred at about the same time that low-grade serum-sickness-like symptoms resolved. There were no measurable increases in tryptase during this period. A similar pattern of changes for venom-specific IgE and IgG was observed for yellow jacket venom (Fig. 2). The patient continues to do well with maintenance venom immunotherapy on a 4- to 6-week basis. He has not experienced any further adverse reactions, and he has tolerated one natural sting (presumed yellow jacket) without systemic reaction.

DISCUSSION

Mueller et al.¹¹ reported no increase in the prevalence of atopic disease in 33 patients with systemic mast cell disorders. However, they did observe a lower total and specific IgE compared with the normal population and suggested that abundant tissue mast cells had absorbed increased amounts of IgE. Raising the question of a relative mast cell or end organ refractory state in SMCD, Keffer et al.¹² went on to show no differences in response to either histamine or morphine skin testing.

We are aware of only a limited number of reports on patients with SMCD and insect sting anaphylaxis. Mueller et al.¹³ in 1983 reported three patients with anaphylactic symptoms after bee stings but no serologic evidence of venom-specific IgE, only two of the three had positive skin test results. The potential causes of anaphylaxis in this setting should certainly include IgE venom immune complexes on mast cell surfaces with no serum IgE because of the previously mentioned absorption phenomenon. Other mechanisms of a clinical reaction include direct toxin-mediated mast cell activation, particularly with multiple stings or spontaneous, labile responses, which can be seen in patients with mastocytosis. Price and Saffko¹⁴ also reported a case of urticaria pigmentosa treated with routine venom immunotherapy with no complications. However, this patient committed suicide relatively early in the course of therapy so no long-term follow-up data were available.¹⁴

Our experience and review of the literature suggested that patients with mastocytosis can and do present with classic anaphylaxis after Hymenoptera stings. This type of antigen-specific reaction must be differentiated from disease-related spontaneous episodes, especially if signs and symptoms are more subtle. In order to document venom-specific IgE, RAST may be the only option if the patient cannot safely tolerate stopping administration of H₁ antagonists. Even if the RAST result is negative, significant levels of venom-specific IgE may still be present at the tissue level. Only after considering the benefit/risk ratio for a given patient can venom immunotherapy be safely administered. For certain patients, controlled anaphylaxis in the setting of therapeutic desensitization with medical personnel available is preferable to unanticipated natural sting reactions. Rush venom immunotherapy may be a reasonable and safe alternative to routine, slower schedules. Rush therapy decreases the time of corticosteroid

pretreatment during the early phases of immunotherapy when higher levels of venom-specific IgE are evident. A rush schedule appears to decrease the phase of increased antigen-specific IgE levels associated with venom immunotherapy, which may persist for up to a year with slower routine schedules. Corticosteroid therapy in conjunction with administration of H₁ and H₂ antagonists appeared to decrease the morbidity (particularly the severity of the delayed large local reactions and postinjection malaise, myalgias, and arthralgias) associated with the early phase of rush venom immunotherapy and did not interfere with the development of protective levels of venom-specific IgG in our patient. Our experience suggests that with adequate precautions, venom immunotherapy, even in a rush schedule, can be successfully administered to patients with SMCD.

We thank Mrs. Mimi Kotwal and Mrs. Joyce Hershey for editorial assistance.

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Allergic contact dermatomucositis to budesonide

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Although previously considered rare, recent evidence^{1, 2} shows that corticosteroid-induced allergic contact dermatitis is much more common than originally thought. Since 1981,³ budesonide has been one of the steroid molecules most widely implicated in allergic contact dermatitis although only occasionally for its use in aerosol form.⁴⁻⁶ We report a case of contact dermatitis caused by budesonide in a nasal spray, the signs of which were intense nasopharyngitis and distant skin eruption (dermatomucositis).

CASE REPORT

A 43-year-old woman who had nonallergic rhinitis with eosinophilia syndrome was treated twice a day with topical budesonide in nasal spray form (Rhinocort Aqua-R; Astra-IFESA S.A., Barcelona, Spain). Ten days later, with sore throat and worsened rhinitis, she went to her general practitioner who prescribed amoxicillin and acetaminophen with the suspicion that the patient had acute pharyngotonsillitis. After another 3 days, a highly pruritic erythematous papular eruption developed on the patient's neck and chest. She discontinued all medication, including the nasal spray, and the clinical symptoms disappeared in 7 days with no treatment; no adverse events were noted. One month later, budesonide treatment was reintroduced, and within 24 hours, she experienced an intensive worsening of her rhinitis with endonasal pain andodynophagia and repeat flare-up of the erythematous papular skin

lesions, which measured approximately 1 cm in diameter and appeared on her neck, chest, and anterior abdomen. The patient was referred to our service, where contact dermatitis caused by budesonide was suspected.

Physical examination revealed intense erythema and edema of the nasal, pharyngeal, and tonsillar mucosa and a fixed, nonscaling, erythematous papular eruption on the patient's neck, chest, and anterior abdomen. There were no eczematous lesions in the nares, on the lips, or in any other region.

Administration of budesonide was discontinued, and 1 month later, epicutaneous tests were carried out with the standard European panel and a second panel with the suspected agent and a series of corticosteroids including pure budesonide (Astra, Lund, Sweden) in several different vehicles (Table I). Challenge tests with amoxicillin, acetaminophen, three systemic steroids, and two topical steroids were subsequently performed.

RESULTS

Results of the standard European panel of tests performed with the Finn Chamber method were negative. All of the budesonide concentrations tested produced negative results at 24 and 72 hours, but highly positive results (confluent erythema, edema, and blisters over a much broader area—5 cm—than that of the 0.5 cm disk used for the patch test) at 120 hours, persisting even after 7 days. The rest of the steroids tested showed negative results. Five healthy control subjects and five patients with nickel contact dermatitis were tested with budesonide, administered in the same vehicles and at the same concentrations; and results were negative.

On the other hand, the patient tolerated optimal systemic doses of amoxicillin (750 mg, by mouth), acetaminophen (500 mg, by mouth), hydrocortisone (250 mg, intravenously), dexamethasone

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J ALLERGY CLIN IMMUNOL 1994;94:559-60

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0091-6749/94 \$3.00 + 0 1/54/56600