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Anaphylaxis after contact with a jellyfish

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We report a case of an anaphylactic reaction to a jellyfish sting. The episode was manifested by hypotension and bronchospasm. The patient's basophils released histamine in response to nematocyst venom from the Chesapeake Bay sea nettle; this sensitivity could be passively transferred by a heat labile serum factor. This appears to be the first case report of such a reaction. (J ALLERGY CLIN IMMUNOL 75:672-5, 1985.)

The classic experiments of Portier and Richet,¹ who induced anaphylaxis in dogs with repeated injections of coelenterate protein, represent the beginnings of

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Abbreviations used

MTNV: Mixed tentacle nematocyst venom
 D₂O: Deuterium oxide
 Anti-IgE: goat anti-human IgE

the scientific study of allergic disease. In spite of the fact that these investigations pointed out the potential for such reactions, there have been no laboratory-based clear demonstrations of human anaphylaxis after jellyfish stings. It has been generally assumed that the anecdotal case reports of severe reactions, and even death, after multiple jellyfish stings were largely toxic responses to the venomous nematocyst proteins.²

Hartman et al.³ have recently reported an elevated IgE antibody concentration against the nematocyst venom of the Chesapeake sea nettle (*Chrysaora quinquecirrha*) in two patients. Both had unusually severe reactions, but neither were believed to have experienced anaphylaxis.

A number of investigators have partially characterized the proteins contained in jellyfish nematocysts and have demonstrated them to be potent neurotoxins and hemolysins.⁴ Uvnäs⁵ first demonstrated that the nematocysts venom from the jellyfish (*Cyanea capillata*) could cause histamine release from rat mast cells, and this observation has been confirmed for other coelenterates by other investigators. This release process was, however, demonstrated by Flowers and Hessinger⁶ to be via a cytotoxic mechanism.

We here report what we believe is the first definitive case of anaphylaxis induced by jellyfish envenomation. The case was manifest in vivo by a classic anaphylactic reaction after a single sting. It was demonstrated, in vitro, that the patient's basophils responded to jellyfish toxin at concentrations that did not affect normal basophils. Furthermore, this jellyfish venom sensitivity could be transferred to normal basophils by a heat labile factor present in the patient's serum.

Case report

The patient was a healthy 59-yr-old woman who suffered only from mild hypertension, which was controlled by a β -adrenergic blocking agent. Neither she nor her family had a history of inhalant allergy or allergic reactions to either drugs or insect stings. In particular there was no known family history of unusual reactions to jellyfish stings.

She has been stung by jellyfish only in Greece, where she resides. The first stings, which were characterized only by minor, painful lesions, occurred 6 to 7 yr ago. Shortly thereafter the patient began to variably develop large local reactions after a sting. The initial response would fade to be replaced within hours by local edema, erythema, and warmth that would peak at 12 to 24 hr. These symptoms resembled, in all respects, the large local reactions observed in sensitive patients stung by insects. On occasion the patient experienced an immediate feeling of weakness after being stung, but there were never objective signs indicating hypotension or respiratory distress.

According to her Greek physician's report as well as to her personal interview, she received a single sting on the back of her knee while she was swimming in the Mediterranean approximately 9 mo before being observed at The Johns Hopkins Center for Allergic Diseases. The offending animal was not captured but was recognized to have tentacles. Within 5 min after envenomation, she began to experience generalized malaise followed by weakness, trembling, and, within 10 min, had clear dyspnea related to the

lower respiratory tract. There was no indication of laryngeal edema. Shortly thereafter, her vision began to fade, and she lapsed into unconsciousness within 15 min of the sting. Observers stated that her lips appeared blue, and her eyes rolled back as if she were in a seizure. She was observed almost immediately thereafter by a physician who, finding no pulse or blood pressure, administered an unknown injection. Recovery occurred within several minutes, at which time she had severe, uncontrolled diarrhea and nausea. A systolic blood pressure of 70 mm Hg was noted as she was transferred into an ambulance for the trip to a hospital. During this trip her blood pressure apparently again became unobtainable and, once in hospital, several hours were required to bring her blood pressure under control. She made an uneventful recovery.

MATERIAL AND METHODS

Adult sea nettle medusae were collected from the mouth of Meredith Creek, St. Margaret's, Md., in the summer of 1982. Crude mixed tentacle nematocyst venom (MTNV) was prepared according to the technique of Burnett and Gould.⁷ The MTNV contained 20 mg of protein and 100 mouse lethal units per milliliter. A mouse lethal unit was defined as that amount of venom protein that would kill all tested 20 gm mice within 48 hr after intravenous challenge.

The assays of histamine release from the patient's leukocytes were carried out as previously described.^{8,9} We used the technique of Pruzansky et al.¹⁰ for the in vitro passive sensitization studies, eluting the native IgE in pH 4 lactate buffer with 5 min of incubation and sensitizing with the patient's serum. Time of sensitization was 60 min at 37° C followed by two washing steps with PAG buffer containing PIPES (Sigma Chemical, Co., St. Louis, Mo.), albumin, and glucose. Subsequently, histamine release experiments were performed. Both active histamine release and release after passive sensitization were carried out with and without the use of a 44% D₂O solution.¹¹

RESULTS

The patient's basophils responded marginally to both anti-IgE and MTNV in the absence of D₂O. In the presence of D₂O, there was 14% histamine release to anti-IgE and a similar response to the MTNV (Fig. 1). The patient's basophils reacted to submicrogram amounts of MTNV with peak histamine release at about 1 μ g of venom protein per milliliter. Note that as the concentration of either anti-IgE or MTNV was increased, the histamine release decreased. This is typical of responses to allergens and strongly indicates that the mediator release induced by jellyfish proteins is not a cytotoxic reaction. Note also that the jellyfish preparation caused no histamine release from the basophils of three normal individuals at any concentration used regardless of the use of D₂O. These subjects' basophils yielded a typical histamine-release curve when basophils were challenged with anti-IgE.

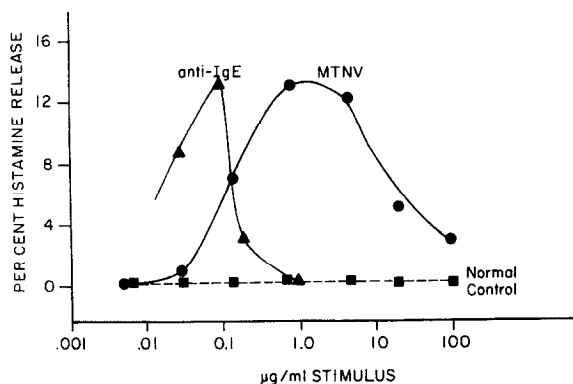


FIG. 1. Histamine release from the patient's basophils by MTNV (●) and anti-IgE antibody (▲). Normal control cells (■) did not respond to any concentration of MTNV.

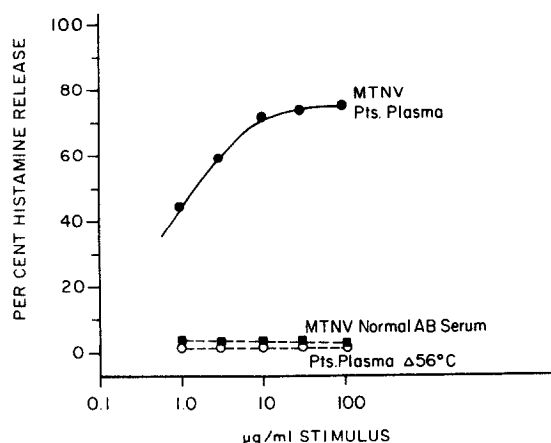


FIG. 2. Histamine release to MTNV after passive sensitization of normal basophils with the patient's plasma (●). No release occurred after sensitization with normal serum (■) or with the patient's plasma that had been heated to 56° C for 4 hr (○).

Passive sensitization experiments with three different donors were conducted to demonstrate that the patient's serum contained IgE antibodies against the MTNV. Fig. 2 demonstrates that, before passive sensitization, the basophils of a normal recipient did not respond to MTNV. After passive sensitization with the patient's serum, there was a marked response with maximal histamine release at 18 µg/ml of venom protein. Finally, heating the patient's serum to 56° C for 4 hr completely abolished the transfer of sensitivity to MTNV to normal basophils. Maximal histamine release after passive sensitization in the other two subjects occurred at a concentration of 10 µg/ml of toxin and was 50% and 5%, respectively.

Discussion

Although many cases of toxic reactions to jellyfish have been reported, we believe that the present case

represents an anaphylactic reaction for two reasons. First, most toxic reactions involving systemic symptoms follow relatively massive contact with jellyfish tentacles.¹ Endean¹² estimated that a fatal envenomation from the very toxic *Chironex fleckeri*, or box jellyfish, in adult humans would require contact with 17.5 m of tentacles. This jellyfish that exists only in Australian waters is far more toxic than any of the Mediterranean coelenterates, and our patient was stung only a single time over a very limited portion of her body surface. Second, her clinical history is a classic example of anaphylaxis.

The impression that anaphylaxis was paramount in this case was strengthened by the laboratory findings. The patient's basophils responded to the jellyfish venom proteins, whereas cells of normal individuals, at concentrations ranging from 5×10^2 to 5×10^{-2} µg/ml did not. This sensitivity could be transferred by the patient's serum to normal basophils, a characteristic of only IgE antibody. The concentration of antigen needed to induce maximal histamine release from passively sensitized basophils was about 10 times higher than that causing maximal release from the patient's basophils, which is a common feature of this procedure. Finally, the ability to passively sensitize normal cells was lost on heating to 56° C, a procedure known to destroy IgE antibodies. We have, indeed, demonstrated that the patient has IgE antibodies to jellyfish venom proteins by RAST but do not have sufficient experience with other types of patients to comment on the significance of these data.

One interesting feature of this case was the development of "large local" reactions on several occasions before the anaphylactogenic sting. Based on the clinical history, this response was entirely similar to the large local reactions to insect stings observed in insect-sensitive patients who, rarely, go on to develop systemic reactions. Although persistent reactions after jellyfish stings have been reported,¹ it has not been generally appreciated that these may be mediated by IgE antibody.

The severity of the anaphylactic reaction may have been potentiated by the fact that the patient was under β-adrenergic blockade treatment. Several articles in the literature postulate such an effect of β-blockers,¹³ and several animal models have been used to confirm these observations.¹⁴ Yet, definite laboratory evidence in humans has not been available.

The exact species of the offending medusa is not known. Although the sea nettle is worldwide in its distribution, it is not a common jellyfish in Greek waters. A more probable cause of the envenomation reported here would be *Pelagia noctiluca*, a jellyfish that has a close morphologic resemblance to the sea

nettle and is very abundant in that location at that time of the year. We cannot, however, exclude the possibility of *Physalia*, another dangerous hydrozoan of the Mediterranean, being the offending agent. Nevertheless, it is not surprising that the patient, who was stung in Mediterranean waters, responded in vitro to the venom of Chesapeake Bay sea nettle (*Chrysaora quinquecirrha*). Both specific and cross-reacting IgG and IgE antibodies have been reported in patients envenomated by jellyfish such as the sea nettle and Portuguese man-of-war.¹⁵ Although a number of investigators are studying the proteins obtained from the nematocysts of these several animals, the antigenic relationships, and certainly the allergenic relationships, are not yet clear.

It remains to be observed how prevalent problem coelenterate venom allergy will be. In spite of a lack of published confirmatory literature, conversations with marine biologists engaged in jellyfish research indicate that reactions to jellyfish venoms that could be allergic in nature are not rare. Some of the sudden "drowning" deaths of healthy swimmers could have resulted from jellyfish stings. The tools to study the prevalence of such sensitivity to jellyfish venom proteins are now available.

The present patient was referred to us for possible preventive immunotherapy. This is entirely feasible on theoretic grounds; whether such treatment is indicated for a disease that is completely preventable by avoiding the sea is open to question.

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