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Iatrogenic pseudoanaphylaxis

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A nurse exposed accidentally to chymopapain by ocular exposure was treated vigorously for chymopapain anaphylaxis. Retrospective analysis of the case indicates that there was no evidence of IgE antibody against chymopapain, and the clinical events were inconsistent with anaphylaxis and could be explained by a vasovagal reaction and the cardiorespiratory effects of repeated intravenous epinephrine. Our assessment is that the nurse is currently in a state of good health; however, she did not accept our absence of allergic disease diagnosis and has sought "clinical ecology therapy." Although no litigation in this case has arisen, the legal implications of this case report are reviewed. (J ALLERGY CLIN IMMUNOL 1987;79:24-6.)

Antigen-induced, IgE-mediated, systemic reactions are the most commonly recognized cases of anaphylaxis.¹ Examples of reactions that may occur without IgE antibody include those caused by radiographic contrast media,² exercise,³ or idiopathic reactions.⁴ Chymopapain, a proteolytic enzyme used for intradiscal injection in patients with documented herniated lumbar intervertebral discs, has been associated with IgE-mediated anaphylaxis.⁵ We report a reaction re-

peatedly interpreted as an acute severe anaphylactic reaction caused by ocular exposure to chymopapain, but in fact, we believe that it was not. Furthermore, some of the clinical signs and symptoms may have resulted from the therapy for presumed anaphylaxis.

Case report

A 37-year-old nurse called the Northwestern University Allergy Service expressing serious concern about her health 10 weeks after what she said was a severe allergic reaction to chymopapain. After this episode, she had persistent symptoms that included feelings of chest tightness, palpitations, and anxiety. She was afraid to eat various foods. One additional emergency admission for non-organic disease had occurred.

The initial event occurred when she was squirted in the eye with chymopapain during a nucleolysis procedure in a hospital operating room. She immediately felt "uncomfortable" and went to the surgical recovery unit where

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Table I. Summary of case analysis that we feel excluded chymopapain anaphylaxis by ocular exposure

- I. Diagnoses elsewhere: anaphylaxis caused by ocular chymopapain exposure, pulmonary edema, and ventricular tachycardia
- II. Significant additional information
 - A. Although the patient wore contact lenses cleaned with solutions containing papain (the crude material from which chymopapain is obtained) up until the time of reaction, there was no history of conjunctivitis.
 - B. There was no conjunctivitis in the exposed eye at the time of accidental chymopapain exposure.
 - C. There was no urticaria, angioedema, asthma, or generalized pruritus during the acute event.
 - D. Hypotension was accompanied by bradycardia until the first of at least three doses of intravenous epinephrine was administered.
 - E. A commercial RAST for chymopapain on patient serum was reported as negative by the patient's internist.
 - F. ELISA for IgE to chymopapain was negative.
- III. Our diagnosis: vasovagal reaction followed by pulmonary edema and episodic ventricular tachycardia caused by repeated intravenous epinephrine

she clutched an anesthesiologist and collapsed. She was found to be hypotensive, and a physician in attendance reported her pulse as bradycardic. She was treated with diphenhydramine, repeated doses of epinephrine intravenously (1:10,000), intravenous hydrocortisone, cimetidine, and oxygen. During the episode, she developed pulmonary edema and supraventricular tachycardia with periods of ventricular tachycardia. The patient was then transferred to the hospital intensive care unit with the diagnosis of chymopapain anaphylaxis. The patient recovered and was discharged after 3 days of hospitalization. All physicians and the patient were totally convinced that chymopapain anaphylaxis was the primary diagnosis.

Clinical analysis

Our initial impression was that the diagnosis of chymopapain anaphylaxis was probably correct. We were doubtful only because anaphylaxis was believed to have been caused by chymopapain exposure through an ocular route. Although local ocular symptoms and sensitization to chymopapain and papain have been reported from exposure to papain in contact lens cleaning solution,⁶ we were unaware of any previous medical reports of anaphylaxis caused by ocular exposure to any antigen.

Through patient history and review of medical records, additional information was obtained that was not consistent with chymopapain anaphylaxis through an ocular route. Al-

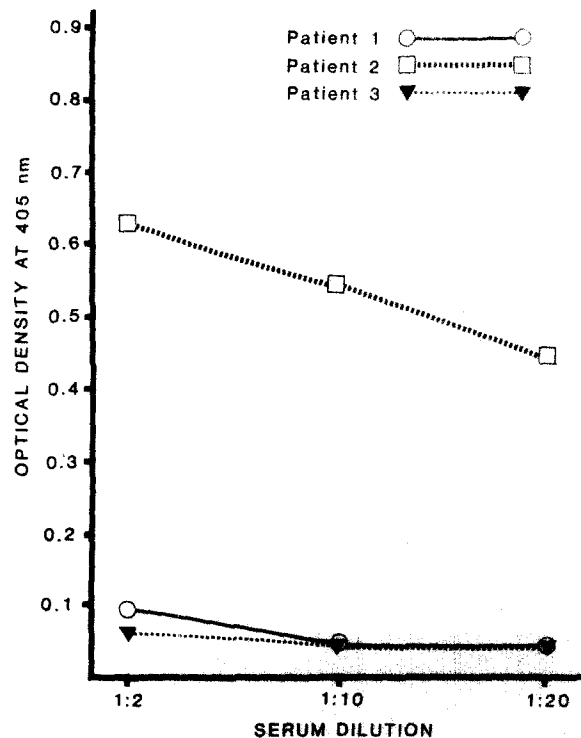


Fig. 1. Levels of IgE to chymopapain, as determined by ELISA. Patient 1 is described in this case report. Patient 2 had chymopapain anaphylaxis 2 weeks before the serum sample was obtained. Patient 3 is a normal control subject.

though the patient wore contact lenses cleaned with solutions containing papain (the crude material from which chymopapain is obtained) up until the time of reaction, there was no history of conjunctivitis that would suggest prior sensitization to chymopapain. In addition, there was no conjunctivitis in the exposed eye at the time of accidental chymopapain exposure.

During the acute event, hypotension was accompanied by bradycardia, not tachycardia that would be expected with anaphylaxis, until the first of at least three doses of intravenous epinephrine was administered. In addition, there was no urticaria, angioedema, asthma, or generalized pruritus during the acute event that would suggest anaphylaxis (Table I).

Laboratory analysis

A commercial RAST for IgE to chymopapain on patient serum was reported as negative by the patient's internist. We performed ELISA analysis for IgE to chymopapain as previously described.⁶ Briefly, the following reagents were added in sequence to microtiter plates with appropriate wastes and incubation periods: chymopapain (0.4 mg/ml), dilutions of patient sera, rabbit antihuman IgE, alkaline phosphatase-conjugated goat antirabbit IgG, and p-nitrophenyl phosphate. The optical density of each well was then read at 405 nm on an automated ELISA reader. ELISA for IgE to chymopapain was performed by three different lab-

oratory investigators at Northwestern and replicated each other. Results are presented in Fig. 1 (Table I).

Case follow-up

Our opinion was not accepted by the patient who sought further care from a "clinical ecologist." Our requests for further information regarding the emergency therapy (e.g., volume of the repeated doses of 1:10,000 intravenous epinephrine) have not been answered by the attending physicians. In spite of the negative RAST and ELISA assays for IgE antibody and our extensive experience with chymopapain skin testing,⁵ the patient refused skin testing on the advice of her physicians.

DISCUSSION

Health care personnel using chymopapain for chemonucleolysis are aware of the risk of anaphylaxis. Anaphylactic sensitivity caused by IgE antibody against chymopapain is present in an estimated 1% of the population.^{7,8} Surgical teams performing nucleolysis are prepared to treat this chymopapain anaphylaxis. In our opinion, the nurse in this case, aware of the risk of anaphylaxis, was frightened by the ocular exposure, sought medical help, had a vasovagal reaction in a surgical recovery unit, and was treated for anaphylaxis. We do not consider this presumptive diagnosis and therapeutic action inappropriate, as delay in treatment of anaphylaxis may be fatal. It is only in retrospect with all of the information available to us that we conclude that the patient had a vasovagal reaction with hypotension and bradycardia and then developed supraventricular and ventricular tachycardia and pulmonary edema caused by repeated use of intravenous epinephrine.

The development of tachycardia and cardiac arrhythmias from large doses of intravenous epinephrine has been well described, although the reasons for this are multifactorial.⁹ Pulmonary edema can result from large doses of epinephrine and has been ascribed to several possible mechanisms including (1) peripheral vasoconstriction resulting in a blood volume shift to pulmonary vascular beds, (2) cardiac failure resulting from both increased peripheral resistance and tachycardia with a resultant decrease in diastolic filling time, (3) an increase in left atrial pressure and/or pulmonary vasoconstriction causing large rises in pulmonary vascular pressures, and (4) central nervous system mechanisms.⁹⁻¹⁵ Intravenous epinephrine (1 ml of 1:10,000) may be used in extreme anaphylactic reactions, but extremely cautious use is warranted.

The authors are unaware of any litigation regarding the accidental exposure and the subsequent treatment. Since the incident presumably occurred during the course of the nurse's employment, the incident would be considered "work related" and therefore fall

within the Workers' Compensation Act.¹⁶ The act establishes a system under which employers are obligated to compensate their employees for work-related "injuries" and also provides an employee a remedy against his or her employer for injuries arising out of that occurring during the course of employment.¹⁷ In Illinois, this remedy is "exclusive" in that it precludes other litigation.¹⁸ The Illinois Supreme Court has ruled that the exclusivity of the act applies even when the alleged injury is caused by the intentional or accidental act of another employee.¹⁹ Even if one or more of the individuals were not considered employees or agents, because the occurrence was "accidental" and not "negligent," the nurse should not be able to pursue a personal injury action against such individuals.

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