

Local ocular anaphylaxis to papain enzyme contained in a contact lens cleansing solution

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This is a case report of a patient who developed IgE-mediated sensitization and subsequently ocular angioedema and conjunctivitis from papain contained in a commercial contact lens cleansing solution. Serum-specific IgE and positive cutaneous prick tests to papain and chymopapain were detected. When the lens solution containing papain was stopped, there was resolution of her allergic symptoms. Recognition of this route of papain-induced sensitization may be important in those patients undergoing chemonucleolysis with chymopapain who may be at greater risk to develop a systemic allergic reaction after injection of this enzyme. (J ALLERGY CLIN IMMUNOL 74:258-60, 1984.)

Papain, a proteolytic enzyme obtained from papaya, is used widely in the chemical, food, and pharmaceutical industries. Allergic sensitization and IgE-mediated occupational asthma induced by papain can occur in chemical workers who are exposed to enzyme dust.^{1, 2} Chymopapain has recently been approved by the Food and Drug Administration for intradiscal injection and dissolution of herniated lumbar discs (chemonucleolysis). The incidence of systemic anaphylaxis after this procedure is 1%, and an anaphylactic death rate of 0.15% has been reported.³ Prick skin testing with papain and immunoassays that measure specific IgE against this enzyme have been developed as reliable methods for the diagnosis of respiratory sensitization to papain in chemical workers.⁴ The sensitivity and specificity of these tests for identifying individuals presensitized to chymopapain before chemonucleolysis are currently being investigated.⁵ Sensitization may also occur after oral ingestion of papain contained in meat tenderizer, papaya fruit, or natural health foods. Anaphylaxis after oral ingestion of papain contained in Adolph's meat tenderizer has recently been reported.⁶ Here we present clinical and immunologic studies performed in a patient who developed allergic ocular and conjunctival

Abbreviations used

PBS: Phosphate-buffered saline
PMSF: Phenylmethylsulfonylfluoride

symptoms associated with exposure to papain contained in a contact lens cleansing product.

Case report

D. H., a 31-yr-old white woman, presented with a 7-month history of chronic ocular pruritus, lacrimation, and episodic periorbital angioedema. For 1 yr before the onset of her symptoms, she used a commercial contact soft lens cleansing solution containing papain on a weekly basis. The enzymatic cleansing solution was prepared by dissolving a tablet of papain (Softlens, Bausch and Lomb, Rochester, N. Y.) in a saline solution preserved with 0.001% thiomerosal and edetate disodium. On each of the previous six occasions that she used this solution for lens cleansing, she experienced severe unilateral or bilateral ocular and periorbital angioedema within 4 hr. Subsequently, she also noted persistent pruritus and lacrimation associated with wearing her lenses.

Although there was a childhood history of seasonal allergic rhinitis treated by specific immunotherapy for 5 yr, the patient denied any recent recurrence of seasonal allergic nasal or bronchial symptoms. There was no history of significant exposure or adverse reactions to meat tenderizer or papaya. Physical examination revealed conjunctival injection with mild follicular changes. Nasal turbinates were pink and nonedematous. Chest examination was clear to percussion and auscultation. A complete blood count demonstrated a hemoglobin of 12.7 gm/dL and a white cell

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TABLE I. Results of specific IgE studies

Route of sensitization	Papain RAST	Chymopapain RAST	Papain skin test (1 mg/ml)	Chymopapain skin test (1 mg/ml)
1 Ocular	10	10	+	+
2 Parenteral	15	17	+	+
3 Oral*	26	27	+	ND
4 Unknown*	22	22	+	ND
Negative controls	4 (SD $\pm$ 0)	4 (SD $\pm$ 0)	—	—

Results are expressed as percent binding of ^{125}I -labeled anti-IgE in patient 1, D. H., in skin test positive controls sensitized via different routes (subjects 2, 3, 4), and in five skin test negative asymptomatic subjects. Subjects 1 and 3 were clinically sensitized to papain, and subject 2 to chymopapain.

ND = not done.

*Serum kindly supplied by Dr. L. E. Mansfield.

count of 7700 with a differential count of 71% segmented neutrophils, 26% lymphocytes, 2% mononuclear cells, and 1% eosinophils. The serum total IgE was 76 IU/ml. Prick and intracutaneous skin testing to a battery of common aeroallergens, which included mold, dust, and the pollens of tree, grass, and ragweed revealed positive intracutaneous reactivity (10^{-3} gm/ml) only to ragweed. Because the patient's symptoms were not seasonal in nature, ocular sensitization to a constituent of the lens solution was suspected. After the lens cleansing solution containing papain was stopped, prompt resolution of ocular itching and lacrimation was noted, and the patient has experienced no further episodes of angioedema.

METHODS

Skin test reagents were prepared with papain and chymopapain (Sigma Chemical Co., St. Louis, Mo.) in PBS (pH 7.4) at a concentration of 10 mg per milliliter and sterilized through a 0.45μ Millipore filter (Millipore Corp., Bedford, Mass.). An aliquot of each preparation was inactivated by boiling at 100°C for 10 min and another aliquot by chemical treatment with PMSF, and both were sterilized for skin testing. Previously, our laboratory had demonstrated that PMSF chemical inactivation did not destroy allergenic determinants of enzymes.⁷ After sterilization, serial tenfold dilutions of each of these reagents were prepared. Skin testing by use of the prick test titration method with tenfold decreasing dilutions of the chemically and heat-inactivated papain and chymopapain reagents was performed in the patient and control subjects; a positive test was defined as a wheal larger than 4 mm in diameter with erythema. The commercial lens cleansing agent, which is packaged as a papain tablet containing no other ingredients, was ground, dissolved in PBS to make a 1 mg/ml solution, sterilized, and used for prick testing. A prick test was also performed with the commercial saline diluent that the patient used to dissolve the papain tablet. Specific IgE in the serum was measured by use of a modified RAST assay.⁸ Papain and chymopapain were bound to methylcellulose discs activated by cyanogen bromide, and the discs were then treated successively three times with 0.1M ethanolamine at 15-minute

intervals followed by washing with PBS. After incubation of the test serum with chymopapain discs and subsequent washing with PBS, 50,000 cpm of ^{125}I -labeled horse anti-human IgE was added. Specific IgE was expressed as percent binding or the ratio of cpm of ^{125}I -labeled anti-IgE bound to the test sample to total cpm added to the test tube multiplied by 100.

RESULTS

Skin prick tests performed with untreated chemically and heat-inactivated papain and chymopapain reagents were all positive at the 1 mg/ml concentration (Table I). Skin prick test titration with the PMSF-inactivated chymopapain exhibited a positive wheal-and-flare response at a concentration as low as 0.01 mg/ml. A positive prick test was detected to a 1 mg/ml of sterile PBS solution of the Softlens papain tablet. Control prick tests in patient D. H. to the commercially preserved saline diluent solution and PBS were negative. A chymopapain-sensitive positive control had cutaneous reactivity to both papain and chymopapain. Specific-IgE studies (Table I) performed in this patient demonstrated RAST binding to both papain and chymopapain. Positive control subjects 2 and 3 who were sensitized via the parenteral route to chymopapain and the oral route to papain, respectively, were studied. They also exhibited elevated serum-specific IgE binding to both papain and chymopapain substrates.

DISCUSSION

Sensitization to papain has been documented to occur as a result of inhalation and oral ingestion of the enzyme. In this case systemic ocular IgE-mediated sensitization to papain was documented by skin and specific-IgE serologic tests in a patient who developed local allergic conjunctivitis and ocular angioedema after local exposure to this enzyme. Because the pa-

tient tolerated the lens solution containing papain for a latency period of 1 yr before the development of sensitization, it is unlikely that she had become sensitized by another means. Since the patient was first evaluated during the tree and grass pollinating seasons, the possibility of seasonal allergic conjunctivitis was excluded by the absence of skin test reactivity to trees, grasses, and mold. However, it was noteworthy that she had an atopic background based on history and cutaneous reactivity to ragweed, although ragweed allergic symptoms were no longer active. These observations were consistent with the previous report of an increased risk of allergic respiratory sensitization caused by *Bacillus subtilis* enzymes among atopic detergent workers.⁹ In this case, avoidance of further contact with papain resulted in complete resolution of her symptoms. Sensitization to the preservative agent thiomerosal contained in the commercial saline solvent was excluded by negative cutaneous reactivity to this product.

Although ocular sensitization to papain has not been studied immunologically in the past, we suspect that papain-induced sensitization via contact lens cleansing products may be more common than currently appreciated. Determination of the prevalence of this problem among wearers of soft contact lens may require further study. The results of this clinical experience suggest that patients who have been previously exposed to enzymatic contact lens cleansing agents containing papain and who are current candidates for chemoneucleolysis may be at increased risk for presensitization to the chymopapain. This conclusion is supported by the finding of apparent cutaneous and serologic cross allergenicity between papain and chymopapain in our papain sensitized patient as well as other chymopapain-sensitized patients we have

studied. Physicians should obtain a careful history of previous exposure to contact lenses and commercial papain cleansing solutions in all patients contemplating this procedure. These individuals should be further assessed by chymopapain skin tests and specific-IgE immunoassay before intradiscal therapy.

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