□ CASE REPORT □

Anaphylaxis to Aprotinin in Fibrin Sealant

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Abstract

A 50-year-old man with chronic otitis media was admitted to our hospital for investigation of lung cancer. He had received repeated instillations of fibrin sealant (Bolheal) in myringoplasty 7 times over 12 months. During the lower lobectomy, soon after fibrin sealant was applied to seal bronchopleural fistulas, systolic blood pressure decreased to 60 mmHg. Treatment with epinephrine and dopamine was required until his condition improved 2 days later. The specific IgE antibody was detected for the solution for fibrinogen and factor XIII containing bovine aprotinin. Cross-reactivity between purified aprotinin and the solution was noted by competitive ELISA inhibition tests.
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Key words: anaphylaxis, aprotinin, ELISA inhibition, fibrin sealant, topical use

Introduction

Fibrin sealant, a hemostatic or adhesive material in which a solution of fibrinogen and factor XIII are combined with a solution of thrombin and calcium in order to form a clot, has been used widely in surgical procedures. Here, we report a rare case of anaphylaxis following topical use of fibrin sealant and demonstrate that aprotinin, an antifibrinolytic ingredient, is the causative agent.

Case Report

A 50-year-old man was admitted to our hospital for investigation of an abnormal chest X-ray in January 2004. He had no history of allergic diseases. One year prior to admission, he developed chronic otitis media and treatment was started at a local otolaryngological clinic. Because of perforation of the tympanic membrane and to improve hearing, repeated instillations of fibrin sealant (Bolheal, Kaketsuken, Kumamoto, Japan; dose range: 0.01 to 0.5 ml) were carried out in myringoplasty 7 times over 12 months. There was no adverse reaction after any instillation.

He underwent lower lobectomy under diagnosis of squamous cell carcinoma of the right lung in February 2004. During the surgery, soon after 3 ml of fibrin sealant was applied to seal bronchopleural fistulas, his systolic blood pressure decreased to 60 mmHg. Epinephrine was given immediately and the fibrin sealant was removed as soon as possible by the surgeons. Dopamine was required to maintain blood pressure within the normal ranges until his condition improved 2 days later. Preoperative examination of peripheral blood revealed a WBC of 5,900 */*μl with 2% eosinophils, which changed to 6,200 */*μl with 21% eosinophils on the 21st postoperative day. Cytological study of postoperative pleural fluid showed an eosinophil-dominant character. Total IgE was 1,300 IU/ml. Specific IgE antibodies were positive for house dust mites, moths, cockroaches, and mosquitoes. The fibrin sealant kit (Bolheal, 3 ml) consists of 4 vials: (1) lyophilized human fibrinogen (240 mg) and human factor XIII (225 Units), (2) a solution for fibrinogen and factor XIII containing antifibrinolytic agent, bovine aprotinin (3,000 KIE), (3) lyophilized human thrombin (750 Units), and (4) a solution for thrombin containing calcium chloride (17.7 mg). We measured specific IgE antibodies to each component in the patient's serum on the 9th postoperative day by means of ELISA. The values were expressed as U/ml on the basis of standard serum and a value of >0.35 U/ml was considered positive. The specific IgE antibody was detected only for the solution for fibrinogen and factor XIII (116 U/ml), suggesting the possibility that the aprotinin contained in the solution might be the causative agent of anaphylaxis. To clarify the cross-

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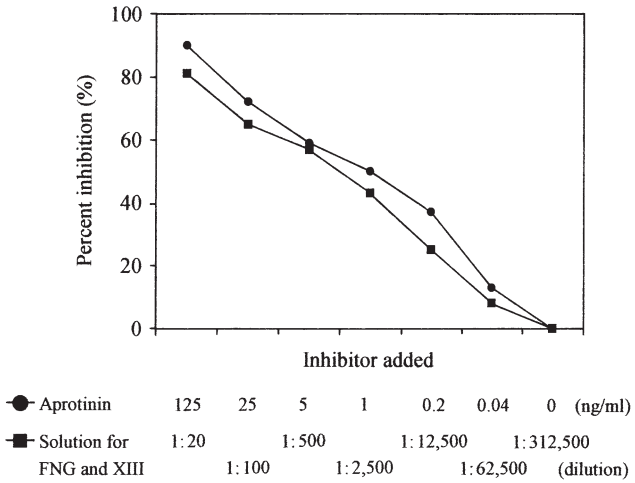

Figure 1. Results of ELISA inhibition with addition of aprotinin and the solution for fibrinogen (FNG) and factor XIII as inhibitors.

reactivity between purified aprotinin and the solution for fibrinogen and factor XIII, competitive ELISA inhibition tests were performed. We prepared purified aprotinin (Wako Pure Chemical Industries, Ltd., Osaka, Japan) at concentrations from 125 to 0.04 ng/ml in five-fold dilutions, five-fold dilutions of the solution for fibrinogen and factor XIII: 1 : 20, 1 : 100, 1 : 500, 1 : 2,500, 1 : 12,500, 1 : 62,500, and 1 : 312,500, and 100-fold diluted serum of the patient. After preincubation with each dilution and serum for 4 hours, specific IgE antibodies were detected and inhibition rates were calculated. As shown in Fig. 1, similar inhibition was noted with purified aprotinin and the solution for fibrinogen and factor XIII, indicating that the aprotinin contained in the solution was the causative agent. We studied serial changes of aprotinin-specific IgE antibody in the patient and whether control subjects had this type of antibody. Control subjects consisted of 26 patients having lung cancer, otolaryngological diseases, pneumothorax, or tuberculoma with previous use of fibrin sealant (Bolheal) and 22 patients having aspergilloma, allergic bronchopulmonary aspergillosis, allergic diseases with normal total IgE values, or normal controls without previous use of fibrin sealant. The patient with aprotinin-induced anaphylaxis had positive IgE antibody for aprotinin (5.43 U/ml) after 7 months. However, no control subject had a positive reaction. Skin tests with the solution for fibrinogen and factor XIII or the purified aprotinin were not performed for fear of systemic reactions.

Discussion

There have been only limited numbers of reports on anaphylaxis following the topical use of fibrin sealant (1–4). Here, we showed that commercial stock solution for fibrinogen and factor XIII in the fibrin sealant kit was cross-reactive to purified aprotinin by ELISA inhibition testing. In general, aprotinin, the only bovine ingredient, is contained in fibrin sealant to prevent lysis of the clot. We speculate that the patient had been sensitized to aprotinin after repeated instillations of fibrin sealant in otolaryngological procedures. Although the patient had allergies to several allergens, atopic status does not appear to be a risk factor in aprotinin-induced anaphylaxis (1–4). A previous report stated that anaphylactic reactions occurred within 3 months after previous exposure, which was consistent with 2 months after the final exposure of this patient (3). We should keep in mind that severe allergic reactions to aprotinin can occur, albeit on rare occasions, in patients with recent topical use of fibrin sealant.

References

1) Kon NF, Masumo H, Nakajima S, Tozawa R, Kimura M, Maeda S. Anaphylactic reaction to aprotinin following topical use of biological tissue sealant. Masui **43**: 1606–1610, 1994.
2) Mitsuhata H, Horiguchi Y, Saitoh J, et al. An anaphylactic reaction to topical fibrin glue. Anesthesiology **81**: 1074–1077, 1994.
3) Scheule AM, Beierlein W, Lorenz H, Ziemer G. Repeated anaphylactic reactions to aprotinin in fibrin sealant. Gastrointest Endosc **48**: 83–85, 1998.
4) Oswald AM, Joly LM, Gury C, Disdet M, Leduc V, Kanny G. Fatal intraoperative anaphylaxis related to aprotinin after local application of fibrin glue. Anesthesiology **99**: 762–763, 2003.