myocardium was critically dependent on flow through the graft. The reason for the persistent and slowly resolving ST changes after transient kinking of the graft is uncertain. Distal emboli or vasospasm are potential but unlikely explanations. The effect of the intravenous nitroglycerin on the time course of ischemia resolution is also speculative. However, no serial ECG or isoenzyme changes diagnostic of acute myocardial infarction developed.

In summary, we describe a patient with previous CABG who had severe myocardial ischemia during mobilization of the right middle lobe before excision of non–small-cell carcinoma. Mechanical manipulation of CABG grafts can occur with subsequent thoracic surgery, and the possibility of graft manipulation should be immediately considered in the differential diagnosis of intraoperative myocardial ischemia. Once the possibility is considered, manipulation should stop, and the graft should be identified and dissected free under direct vision. In this way a potentially devastating intraoperative complication may be avoided.

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An Anaphylactic Reaction to Topical Fibrin Glue

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FATAL drug reactions occur in 0.01% of surgical inpatients. Important among serious adverse drug effects are allergic reactions because of their sudden onset and potential for catastrophic outcome.[1] Fibrin glue, a physiologic glue, has been used in a variety of clinical situations including bleeding after cardiac surgery and vascular anastomosis, organ injury, and neurosurgical procedures.[2–4]

Among the extensive clinical experience to date, there are some reports of adverse reaction to fibrin glue.[5] We describe a case of anaphylactic reaction immediately after topical application of fibrin glue (Ber-

iplast P, Behringwerke AG, Marburg, Hoechst, Japan) used to seal suture holes and an oozing surface after pulmonary lobectomy during general anesthesia.

Case Report

A 67-yr-old woman with metastatic pulmonary cancer was scheduled for right middle and lower lobectomy. Surgical history included cholecystectomy at the age of 37 yr and proctectomy for the cancer at the age of 63 yr. Her medical history was unremarkable. She had no known allergy to drugs or foods and no history of atopy or asthma. Results of analysis of preoperative laboratory data, chest x-ray, and electrocardiogram were normal.

The patient received atropine 0.5 mg and hydroxyzine 50 mg 1 h before the operation. The electrocardiogram was monitored, and radial arterial and venous catheters were placed preoperatively. An epidural catheter was inserted at the T7–T8 interspace. Anesthesia was induced with thiopental 350 mg, and the trachea was intubated with a left-sided double-lumen tube after administration of succinylcholine 40 mg. Anesthesia was maintained with 70% nitrous oxide, 30% oxygen, and 0.5–2.5% sevoflurane. Bupivacaine 0.25% was administered at a rate of 6 $ml \cdot h^{-1}$ *via* the epidural catheter. Vecuronium was given as needed to facilitate surgery. After the surgical incision, the left lung was mechanically ventilated and the right lung allowed to deflate.

On completion of the right middle and lower lobectomy, 3 ml fibrin glue was applied to seal suture holes and an oozing surface. The fibrin glue kit (Beriplast P) consisted of four bottles: (1) lyophilized fibrinogen and factor XIII, (2) aprotinin, (3) lyophilized thrombin, and (4) calcium chloride. The fibrinogen and factor XIII were dissolved in aprotinin, and the thrombin was reconstituted in calcium chloride. The two solutions were then drawn into separate syringes, which were loaded on a double-barreled syringe holder designed to mix and apply the components simultaneously, and the solution was applied to the bleeding sites. Within 3–5 min after application of fibrin glue, systolic blood pressure decreased to 30 mmHg and heart rate decreased to 40 $beats \cdot min^{-1}$. Inhalation of sevoflurane and nitrous oxide and infusion of bupivacaine were discontinued, and 100% oxygen was administered. Because blood pressure was unresponsive to fluid administration and multiple doses of ephedrine (total 16 mg) and atropine (0.5 mg), 0.1 mg epinephrine was given, and continuous infusion of dopamine was initiated at a rate of 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Systolic pressure returned to 105 mmHg approximately 35 min after the initial episode of hypotension. When the operation was completed and drapes were uncovered, diffuse urticaria with generalized flushing was noted on the extremities and the torso. The patient was transferred to the intensive care unit and recovery was uneventful.

The electrocardiogram was not suggestive of myocardial ischemia. An echocardiogram showed slight hyperkinetic motion of the heart and ruled out myocardial infarction. Because of the temporal relation between administration of fibrin glue and hypotension, immunologic studies were ordered. Plasma tryptase concentrations in blood samples obtained after the removal of surgical drapes (approximately 2 h after the initial episode of hypotension) and 5 and 23 h after the initial episode of hypotension were 34.6, 15.3, and less than 2 $ng \cdot ml^{-1}$, respectively. Tryptase concentrations of less than 5 $ng \cdot ml^{-1}$ are considered to be within normal limits, and concentrations greater than 10 $ng \cdot ml^{-1}$ are appreciably increased.[6]

A lymphocyte-stimulation test[7] and histamine-release test were performed 7 weeks after surgery.[8] Vecuronium and fibrin glue (Beriplast P) were tested because these drugs had been given immediately before the adverse reaction occurred. The fibrin glue consists of four bottles containing five components: (1) lyophilized fibrinogen 65–115 $mg \cdot ml^{-1}$ and factor XIII 40–80 $U \cdot ml^{-1}$,# (2) aprotinin 1000 $KIU \cdot ml^{-1}$,** (3) lyophilized thrombin 400–600 $U \cdot ml^{-1}$, and (4) calcium chloride 14.7 $mg \cdot ml^{-1}$.

A lymphocyte-stimulation test was carried out with isolated lymphocytes in the presence of vecuronium and six dilutions of each component of the fibrin glue except calcium chloride. Six dilutions were prepared from commercial stocks: 1:50, 1:250, 1:1,250, 1:6,250, 1:31,250, and 1:156,250. The lymphocyte-stimulation test measures the extent to which mitotic division is initiated in an isolated lymphocyte preparation and then measures the incorporation of added tritium-labeled thymidine into a cell preparation with drugs (experimental) or with solvent (control). Results are expressed as a stimulation index that is considered positive when the experimental stimulated radioactivity (in counts per minute) is more than 200% of that of the nonstimulated control.[7] In this case, the tests revealed that aprotinin induced blast formation of lymphocytes in a dose-independent manner, whereas the other two components and vecuronium did not (fig. 1).

A whole-blood histamine-release test was performed in the presence of various dilutions of aprotinin in the fibrin glue (Beriplast P): 10^{-1}, 10^{-2}, 10^{-3}.[9,10] Results expressed as a percentage of total histamine are considered positive when more than 10% of total histamine has been released. In this case, aprotinin released 72.7%, 47.5%, and 35.2% of total histamine from whole blood in the presence of 10^{-1},

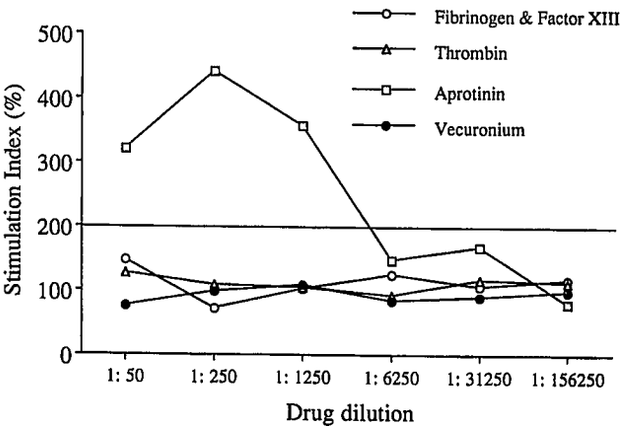

Fig. 1. Lymphocyte-stimulation test with vecuronium and fibrin glue in the presence of six dilutions of these drugs. Results are expressed as a stimulation index, which is considered positive when the value is more than 200% of that in unstimulated lymphocytes.

One U corresponds to a factor XIII activity of 1 ml of fresh citrated plasma (pooled plasma) from healthy donors.

** One KIU is equivalent to 1.111×10^{-3} trypsin inhibitor units.

10^{-2}, and 10^{-3} dilutions of aprotinin, respectively. Skin tests were not performed with these drugs because the data from the two *in vitro* tests were considered sufficient to identify the offending drug. Moreover, the potential risk of skin testing was avoided because only topical application of aprotinin induced a severe anaphylactic reaction in the patient.

Discussion

To our knowledge, three cases of anaphylaxis to fibrin glue have been reported. Milde reported an anaphylactic reaction to fibrin glue in a patient with an immunoglobulin A (IgA) deficiency and increased anti-IgA antibody titers.[11] Berguer *et al.* reported two cases of severe hypotension immediately after the injection of fibrin glue into deep hepatic wounds and concluded that this reaction represents a systemic reaction to bovine thrombin.[5] In our case, aprotinin was the component of fibrin glue that caused anaphylaxis after topical application.

We measured plasma concentration of tryptase because tryptase is liberated into venous blood after mast cell degranulation in an anaphylaxis or anaphylactoid reaction.[6,12] The markedly increased plasma concentrations of tryptase 2 and 5 h after the initial episode of hypotension implicated mast cell activation and degranulation consistent with systemic anaphylaxis.[6,12] To identify the causative drugs, immunologic investigations were carried out 7 weeks later.[8] Results of the lymphocyte-stimulation test and histamine-release test verified that aprotinin was a causative drug in this adverse reaction. The histamine-release test has been used extensively for *in vitro* studies of allergy.[9,13–16] Histamine-release studies using whole blood might better reflect the true *in vivo* immunologic situation because allergic reactions *in vivo* depend not only on circulating immunoglobulin E (IgE) but also on several other factors, including the balance between blocking antibodies and IgE on target cells and chemical mediators released from mast cells or basophils.[9] The concentrations of aprotinin used in the histamine-release tests were relatively large, but 10^{-3} dilution of the drug, which included aprotinin 0.5 KIU $\cdot$ ml^{-1}, showed positive release of histamine. Although mast cells can be activated by non–IgE-mediated events, the data obtained from lymphocyte-stimulation test (fig. 1) suggested an anaphylactic reaction mediated by IgE. However, although previous sensitization is an important component for development of true IgE-mediated anaphylaxis, we verified that aprotinin, thrombin, and fibrin glue had not been used in the earlier operation for rectal cancer.

Catecholamines are a mainstay in the treatment of anaphylaxis.[17] We initially treated the cardiovascular depression by administering fluid, ephedrine, and atropine. Because the initial therapy did not resolve the hypotension, we administered epinephrine, which reversed the cardiovascular depression. The current case again indicates the importance of epinephrine in the therapy of anaphylaxis.

Aprotinin, a polypeptide isolated from bovine lung, is capable of stimulating a specific IgE antibody in humans[18] and has been shown to cause anaphylaxis.[18–21] Wüthrich *et al.* described an IgE-mediated anaphylactic reaction to aprotinin in a boy during cardiac surgery and confirmed antiaprotinin IgE antibody by a radioallergosorbent test.[19] The frequency of hypersensitivity reactions after repeated aprotinin administration is about 10%.†† All previous reports of anaphylaxis due to fibrin glue except for that of a patient with an IgA deficiency show the causative drugs to be the bovine thrombin in the glue.[5,11] Several cases of anaphylaxis after topical application of only bovine thrombin have also been reported.[22–24] Bovine thrombin is a protein substance with a high antigenic potential that may lead to the development of antibody.[22,23] Because both thrombin and aprotinin included in fibrin glue are polypeptides derived from bovine tissue and have high antigenicity, anesthesiologists and surgeons should bear this potential side effect in mind. A prick test or intradermal testing or radioallergosorbent test with thrombin and aprotinin might be considered before repeated administration in patients who have previously been exposed to the drugs.[18,24,25] On administration of aprotinin Levy recommends that a very small, dilute dose (≤ 1 $\mu g \cdot ml^{-1}$) should be administered 10 min before the administration of the loading dose.[25]

In conclusion, we present a case in which fibrin glue induced anaphylaxis after topical application during general anesthesia and in which we identified aprotinin as a causative agent. Measurement of plasma tryptase is recommended to make a differential diagnosis of anaphylaxis or anaphylactoid reaction from other causes that produce sudden hypotension without any clear cause.

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