

Intraoperative anaphylaxis to gelatin-based hemostatic agents: a case report

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Abstract: Surgiflo Haemostatic Matrix is an absorbable gelatin matrix hemostatic material that has been widely used in various surgical operations to assist hemostasis. Nonetheless, as biologically active agents (contains porcine gelatin), there is potential for allergic reactions to these products. Here, we report the case of a 71-year-old man who had intraoperative anaphylaxis with cardiovascular events to gelatin associated with the use of a topical hemostatic agent (Surgiflo). The patient reported a history of red meat allergy and tick bites during his allergological examination after anaphylaxis. He also had high levels of specific IgE antibodies towards alpha-gal. Special consideration should be given before administering bovine- or porcine-derived gelatin products during surgery to patients with animal-related allergies, such as alpha-gal or gelatin allergy and an atopic background.

Keywords: gelatin allergy, alpha-gal allergy, hemostatic agents, anaphylaxis

Introduction

The use of topical Hemostatic Matrix agents such as Gelfoam, FloSeal and SurgiFlo in surgery is common and reduces bleeding during a wide variety of surgical procedures.¹ Such agents work by providing an environment for platelets to adhere and aggregate within, thus building on the patient's natural coagulation cascade. The patient's endogenous thrombin is activated, and the patient's thrombin converts fibrinogen into an insoluble fibrin clot. The thrombin component of Hemostatic matrix provides an ancillary effect to the innate hemostatic property of the flowable gelatin matrix. When used in appropriate amounts, these hemostatic agents are absorbed completely within 4–6 weeks.

Many of these new agents are combined with human thrombin and animal gelatins (bovine and/or porcine gelatin matrix), which has potential for allergic reactions. Gelatin is a denatured protein product made from boiled bovine or porcine hoofs, horns and skin.² The use of this kind of materials must be avoided in patients with known allergies to gelatin. Here, we would like to report a case of an intraoperative anaphylactic reaction to Surgiflo (Hemostatic Matrix; Ethicon Inc, Somerville, NJ, USA), a hemostatic agent containing partially reconstituted porcine gelatin used to decrease surgical bleeding. To our best knowledge, this is the first reported case with intraoperative anaphylaxis secondary to a gelatin allergy observed in Norway.

Case report

A 71-year-old male residing in Bergen, western coast of Norway, was referred to our department (Section for Clinical Allergology, Department of Occupational Diseases)

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because of suspected anaphylaxis secondary to Surgiflo during a surgical operation. He has had chronic obstructive pulmonary disease (COPD) since 2004 and received a diagnosis of Atrial Septal Defect (ASD) later on. He was operated for ASD in October 2017. During the operation, anesthesia was induced with midazolam hydrochloride, fentanyl citrate, thiopental sodium and vecuronium bromide without any complications. The Surgiflo (Human thrombin with porcine hemostatic matrix) was used in the last phase of the operation. The patient had at that timepoint been released from the cardiopulmonary bypass, and SAGMAN blood product, thrombocytes and protamine sulfate had been given, and control of hemostasis confirmed. Shortly after the Surgiflo was placed over the sutures on the outside of the right atrium, hemodynamic instability suddenly occurred. Within 2–3 mins, he experienced rapid onset of hypotension, tachycardia and high airway pressure. The patient was given a bolus-injection 10 mg of ephedrine in the initial phase of the reaction, and then continuous infusion of epinephrine and norepinephrine, initially at rate 0.2 µg/kg/min and 0.7 µg/kg/min, respectively. A bolus dose of epinephrine 0.04 mg was also given. Approximately after 60 mins, the infusion rate of epinephrine and norepinephrine was reduced to 0.1 µg/kg/min. Also, hydrocortisone 200 mg i.v. and dexchlorpheniramine 5 mg i.v. were given. After a while, his vital signs became stable, and surgery was completed successfully. It was also noted that he had erythematous rash on his trunk. Thereafter, he was referred to us for allergological examination against Human Hemostatic Matrix, Surgiflo.

According to atopic background, he had no known history of allergic disease personally or in his first degree relatives. However, he has stated that he could not eat meat when he was between 9 and 19 years old. Three to four hours after intake of meat, he experienced allergic reaction with itching and observed afterwards urticaria on the whole body, especially arms and abdomen, and thick feeling in the throat with moderate dyspnea, but no dizziness, nausea or diarrhea. The patient reported that he was bitten by ticks in a local forest when he was on a trip at the age of 8 years, and a reaction against meat came after this episode. He had no any tick bites since then. Interestingly, this allergic reaction after intake of meat disappeared around the age of 19 years. Currently, the patient may consume meat and meat products without any problems.

We performed allergological examination at our department. Skin prick test with Surgiflo, latex, chlorhexidine, midazolam hydrochloride, fentanyl citrate, thiopental sodium and vecuronium bromide were negative, and

skin prick test using a standard food allergen panel with six allergens (egg white, cow's milk, codfish, wheat flour, peanut and soy) including raw ox, pork and sheep meat were also negative. However, skin prick test with gelatin was positive. Blood samples for specific IgE against ox, pork and lamb were high (sIgE: 3.28; 1.40 and 0.47, respectively; and upper normal limit of sIgE for these are <0.35 kU/L). Moreover, the IgE antibodies specific for alpha-1,3-galactose (alpha-gal) were high (sIgE: 26.6 kU/L). Otherwise, routine blood tests and other allergy parameters in serum such as specific IgE against gelatin, latex, chlorhexidine, standard food allergy panel with six allergens (egg white, cow's milk, codfish, wheat flour, peanut and soy), standard airway panel with eight allergens (birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, cat, dog, and horse) (ALK Abello, Hørsholm, Denmark), and tryptase were within the normal reference range except serum total IgE level was slightly high (153 kU/L). Furthermore, histamine release test (HRT) and basophil activation test (BAT) were conducted to further elucidate the clinical history. HRT was performed according to the producer's protocol (Reflab ApS, Copenhagen, Denmark), with small adjustments. HRT was done twice, first with Surgiflo, then two months later with lamb, beef and pork. In short, the allergen is titrated in an 11 step serial dilution in PIPES puffer. PIPES buffer is used as negative stimuli and anti-IgE is used as a positive control. After the controls and samples are incubated with the patient's blood, the samples are washed, dried and shipped to Reflab in Denmark for histamine measurement. Our in-house BAT is based on incubating a suspected allergen with the patient's heparinized whole blood. BAT was also performed twice, first with Surgiflo, then three months later with Surgiflo and alpha-gal-HSA (Bühlmann Laboratories AG, Scönenbuch, Switzerland). The allergens are dissolved in phosphate-buffered saline (PBS; Sigma Aldrich Norway AS, Oslo, Norway) and using in six 10-fold dilutions in PBS. PBS is also used as a negative control, while anti-FcεR1 (Bühlmann Laboratories AG) provides a positive control. Immediately after the stimuli is added, the cells are stained with a titrated mix of anti-CD63 FITC (Beckman Coulter, Brea, CA, USA), anti-CD123 APC (Miltenyi Biotec, Bergisch Gladbach, Germany), anti-CD193 BV421 (Biolegend, San Diego, CA, USA) and anti-CD203c PE (Beckman Coulter). After 25-min incubation at 37°C, the samples are RBC-lyzed (Agilent Technologies ApS, Glostrup, Denmark), washed (CellWash; BD Biosciences,

Franklin Lakes, NJ, USA) and analyzed on a Canto II flow cytometer (BD Biosciences). Basophils are identified as SSClow, CD193high, and CD123+ events and 250 basophils are collected in each sample. Basophil activation is evaluated by setting a gate at 3% CD63+ and CD203c+ in basophils with negative stimulus. The FcεR1-stimulated basophils must reach $\geq 16\%$, in both CD63 and CD203c in order for the test to be accepted. If either CD63 or CD203c is $< 16\%$, the test is rejected as inconclusive. A sample is considered positive if either CD63 and/or CD203c reach $\geq 16\%$ positive basophils in one or more dilutions of the allergen. Unfortunately, neither HRT nor BAT yielded a positive test result. RefLab interpreted all allergen stimulations negative. Also, the allergens could not induce basophil activation in either of the BATs. At the both times, anti-FcεR1 failed to stimulate the patient's basophils (CD63; 6.4% and 6.8%, CD203c; 6.0% and 2.4%). Therefore, the patient was concluded to be a non-responder.

The patient had alpha-gal allergy induced by tick bites. He had anaphylaxis during surgery after receiving Surgiflo, which contains gelatin from pigs. This reaction could be explained by his high levels of alpha-gal specific IgE antibodies, a carbohydrate that could be present in the porcine-derived gelatin that Surgiflo is based on. He was recommended avoiding exposure to products derived from bovine or porcine gelatin in future operations. The patient provided written informed consent prior to the publication of this case report.

Institutional approval was also obtained to publish the case details.

Discussion

To our best knowledge, this is the first published case to report an intraoperative anaphylaxis secondary to gelatin allergy which has been observed in our country. Even though this is an unusual allergic reaction, intraoperative anaphylaxis against hemostatic agents has been described in few similar cases from other countries in the literature.³⁻⁶

In general, intraoperative anaphylactic reactions are rare, with an estimated incidence of 1:4,000 to 1:25,000. Previously, an anaphylactic reaction to Surgiflo, a hemostatic agent containing partially reconstituted porcine gelatin used to decrease surgical bleeding, has been reported to cause anaphylaxis with sudden and profound hypotension during posterior spinal fusion in an adolescent with a history of repaired truncus arteriosus.⁷ Anaphylactic

reaction to gelatin-containing hemostatic agents have also been reported in the ophthalmic and orthopedic literature, most commonly during scoliosis repair in adolescents.^{2,8} Intraoperative anaphylaxis was observed after intraosseous gelatin administration.⁸

Allergic reaction to gelatin may be immune or non-immune mediated reactions. Immune allergic reactions can be mediated by immunoglobulin E (IgE) or non-IgE mediated.

IgE-mediated (type 1) reactions can be detected with in vitro immunoglobulin testing. Gelatins are high-molecular-weight peptides derived from various animal collagens and are used in several foods, medications, cosmetics and vaccines as stabilizers. Gelatin comes from different sources and has different degrees of allergenicity depending on type of gelatin, its processing, molecular weight, melting point and dosage. Gelatin allergy has been well described in reactions to gummy candy and vaccines, such as measles, mumps and rubella containing gelatin as a stabilizer.⁹ However, there are few publications on its impact in intraoperative anaphylaxis, particularly as a component of surgical hemostatic agents.

The alpha-Gal syndrome is triggered by IgE antibody response against the carbohydrate Galactose-alpha-1,3-galactose, which is present in glycoproteins from tick saliva and tissues of non-carnivorous mammals. The association between tick bites and the development of mammalian meat allergy was first described in 2007 by van Nunen et al. Later, this association was confirmed in 2009 by Commins et al, and they discovered the epitope likely responsible for such allergic reactions (α -Gal).¹⁰ The alpha-Gal syndrome is a regionally common form of food allergy that has a characteristic with delay in symptom onset and can develop at any time in life.¹¹ It has been suggested that tick bites inoculate also other antigens such as gelatin that could potentially sensitize the patient.¹² When the patients avoid successfully further tick bites and red meat, the circulating alpha-gal-specific IgE antibody concentrations diminished over time, as previously observed.¹²

Our patient developed sudden and profound hypotension after receiving Surgiflo. Given that the patient's symptoms were classic for anaphylaxis and that the timing of the anaphylaxis immediately followed the administration of SurgiFlo, we believe that SurgiFlo was the cause of the reactions. Additional allergological examination obtaining detailed medical history (red meat allergy induced by tick bites), positive skin prick test with gelatin, high serum levels of alpha-gal and its relation with gelatin

allergy help support the diagnosis. This patient reminds us of the importance of eliciting a thorough allergy history prior to beginning new therapies. Special care should be taken in the administration of these products, particularly in the atopic individuals, particularly in patients who have a history of gelatin and/or alpha-gal allergy.

A study from Mullins RJ et al showed that there is a relationship between red meat allergy and sensitization to gelatin and galactose-alpha-1,3-galactose (alpha-gal).¹³ They have investigated the clinical significance of gelatin sensitization, the predictive value of a positive test and an examination of the relationship between allergic reactions to red meat and sensitization to gelatin and alpha-gal. The results showed that there was a strong significant correlation between positive gelatin skin tests and serum specific IgE levels of alpha-gal in the patients serum. Furthermore, alpha-gal was detected in bovine gelatin colloids by inhibition radioimmunoassay. They also found asymptomatic sensitization to gelatin, red meat and alpha-gal in a small number of patients with tick bite reactions in another country with different tick species. Overall, they have identified a significant relationship between adult onset red meat allergy and sensitization and clinical reactivity to gelatin. Most patients allergic to red meat were also sensitized to gelatin and a subset was clinically allergic to both. The detection of alpha-gal in gelatin and correlation between the results of alpha-gal and gelatin testing raises the possibility that alpha-gal specific IgE may be the reason for reactivity to gelatin. In our patient, we also found positive skin prick test with gelatin and high level of specific IgE toward alpha-gal in patient's serum in accordance with literature. Thus, meat allergy could represent a risk factor for gelatin allergy.

Conclusion

Prior reactions to gelatin, bovine or porcine products, including immunizations, gelatin, meat allergy (alpha-gal) and gummy candy should be considered a contraindication to the use of gelatin containing hemostatic agents during surgery. In preoperative screening, high serum specific IgE levels of alpha-gal might have a high positive predictive value on possible reactions to hemostatic matrix agents. Therefore, it can be useful to screen for alpha-gal specific IgE antibodies in patients who present an atopic background and medical history

of tick-induced red meat allergy in order to minimize the likelihood of intraoperative cardiovascular events to hemostatic matrix agents.

Disclosure

The authors report no conflicts of interest in this work.

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