



Impact of Newly Emerging Alpha-Gal Allergies on Cardiac Surgery: A Case Series

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Abstract

The influence of alpha-gal allergies on cardiothoracic surgery is largely unknown. Allergic responses to galactose-alpha-1, 3-galactose, or “alpha-gal”, are due to antibodies against non-primate mammalian proteins and are mediated by IgE. This allergy has only recently been discovered and is increasingly prevalent, upwards of 20%-25% of the general population in the southeast United States is sensitized to alpha-gal. Due to the exposure of patients to significant amounts of alpha-gal containing heparin during the course of cardiopulmonary bypass, this allergy may have significant implications for patients undergoing cardiac surgery. We provide a four case series from a single institution detailing successful cardiac surgery in four patients with known alpha gal allergies. These cases demonstrate that pre-treatment with diphenhydramine and steroids may help attenuate serious allergic reactions and allow cardiac surgery to be performed more safely.

Introduction

The impact of increasingly prevalent alpha-gal allergies on cardiothoracic surgery is largely unknown. Galactose-alpha-1, 3-galactose (alpha-gal) is an oligosaccharide epitope found in non-primate mammalian animals. Alpha-gal allergies were first reported in 2007 and now upwards of 20%-25% of the population in the Southeast United States is thought to be sensitized [1,2]. IgE-mediated allergic reactions range from urticaria to anaphylaxis, and delayed onset reactions are common when the antigen must be digested [3]. Triggers for alpha-gal reactions include administration of cetuximab, a monoclonal antibody, or after eating mammalian meat (beef, pork, lamb, etc.) [3,4]. Development of alpha-gal allergies typically occurs in adulthood and is thought to be associated with a bite from the Lone Star tick, *Amblyomma americanum*, which causes an IgE antibody reaction towards the carbohydrate molecule [3,5,6].

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The literature encompassing alpha-gal allergies in cardiothoracic surgery is sparse. A case report by Mozzicato et al. [7] described three patients with suspected alpha-gal allergies, two of which developed immunologic reactions from porcine/bovine aortic valve replacement. Bioprosthetic valves are also thought to undergo early calcification and degeneration due to the alpha-gal allergy. The third patient developed severe anaphylactic shock from an infusion of heparin during an abdominal aortic aneurysm surgery. Heparin is derived from animal products, e.g. porcine intestines, so it is possible that patients with alpha-gal allergies may react to the anticoagulant. Unfortunately, the data on heparin cross-reactivity with alpha-gal is severely lacking.

We present four cases involving premedication and heparin utilization during cardiopulmonary bypass in patients with alpha-gal allergies.

Case Series

Case 1

A 49-year-old female with past medical history of repaired aortic coarctation and alpha-gal allergy was diagnosed with severe aortic stenosis and a calcified bicuspid aortic valve was seen on TTE. Due to progression of her heart failure symptoms, aortic valve replacement was recommended. The patient was diagnosed with her alpha-gal allergy due to reaction consistent with anaphylaxis after eating pork or beef. She developed the allergy after an observed tick bite. The history of alpha-gal allergy raised concern for an anaphylactic response to administration of heparin intraoperatively. Concern for early calcification and dysfunction of a bioprosthetic valve due to her allergy led the patient to choose a mechanical aortic valve.

The patient was admitted preoperatively and was premedicated with 50 mg of prednisone every 8 h and 25 mg of diphenhydramine to decrease the risk of an adverse allergic reaction. After she was anesthetized, she received 125 mg methylprednisolone and 50 mg diphenhydramine prior to administration of systemic heparin. She tolerated the surgery well; her aortic valve was replaced with a 23 mm Sorin bileaflet mechanical aortic valve without complication. No adverse reactions were observed in the post-operative period. Warfarin was started while the patient was still in the ICU. No heparin bridge was used in order to minimize the risk of alpha-gal allergic reaction. The patient was released on post-operative day 4 with no complications.

Case 2

A 63-year-old male with a past medical history of hypertension and diabetes presented to the emergency department with worsening chest pain and was diagnosed with unstable angina. Cardiac catheterization showed 100% mid-left anterior descending (LAD) stenosis, 90% proximal LAD stenosis, and 80% distal right coronary artery (RCA) disease and he was therefore recommended to undergo surgical revascularization.

The patient was diagnosed with an alpha-gal allergy after a tick bite in 2014. He experienced anaphylactic symptoms 6 h after eating a cheeseburger. After repeated episodes of nausea, vomiting, hives over his entire body, hypotension and dizziness several hours after ingesting pork or beef products, the connection was made. He was confirmed to have an alpha-gal allergy by IgE testing. The patient was able to control his symptoms through dietary modification and avoidance of pork and beef products. He reports that he is able to tolerate occasional pork/beef products if he premedicates himself with diphenhydramine, but still does experience mild hives on his arms.

Our local alpha-gal experts were consulted, and a bedside skin test with a 5000-unit test dose of intravenous heparin was performed the day prior to surgery. This test dose was taken from the same vial that would be later used during his surgery. Different lots of heparin are thought to have variable amounts of alpha-gal in them, but there is no way to quantify it at the current time. The bedside test was negative. No steroids or diphenhydramine were given preoperatively. Intraoperatively, the patient was given a starting dose of 27000 units of heparin, as well as 100 mg of prophylactic hydrocortisone.

The patient had successful three vessels Coronary Artery Bypass Grafting (CABG). He had an uneventful postoperative course and was discharged from the hospital on post-operative day 4.

Case 3

A 71-year-old male with a past medical history of hypertension, hyperlipidemia, and coronary artery disease presented to the emergency department after new-onset shortness of breath and chest pain that radiated to his mouth when walking. He was diagnosed with a Non-ST Elevation Myocardial Infarction (NSTEMI) and was taken to the catheterization lab. He was found to have complete occlusion of the RCA and 90% stenosis of the ostial LAD. Cardiac surgery was then consulted and he was scheduled for a 2-vessel CABG. His surgery was performed without complication and he received a 2-vessel CABG with a LIMA to LAD anastomosis and a saphenous vein graft to the PDA.

When the surgical drapes were taken down at the conclusion of

his operation, the patient was noted to have an urticarial rash on his hands. By the time he was transferred this had progressed to a severe full body urticarial rash. Due to concern for an allergic reaction, he was treated with an immediate bolus of 100 mg IV methylprednisolone, followed by 2 mg/kg methylprednisolone twice daily and 12.5 mg IV diphenhydramine every 6 h, both for a total of 72 h postoperatively. Additionally, he was maintained on a low dose epinephrine infusion.

After the allergic reaction was noted, a discussion with the patient's family revealed that the patient had a history of an alpha-gal allergy. Notably, he had received heparin previously without issue. His allergic reaction may have been provoked by administration of a large dose of heparin for cardiopulmonary bypass. Alternatively, Gelfoam (Pfizer, New York, New York, USA), a hemostatic agent made from gelatin and purified porcine skin and used for sternal bleeding, is another possible culprit.

Medical therapy worked to suppress the patient's allergic response. However, on post-operative day zero, he developed persistent ST-elevations and was taken to the cardiac catheterization lab. Catheterization demonstrated acute thrombus present just distal to the LIMA to LAD anastomosis. This area was treated with balloon angioplasty with good result. Several hours later, he developed ST changes again and returned to the catheterization lab. No thrombus or blockages were found at that time; all the bypass grafts were patent. Following this, the patient did well and had an uneventful course. He was discharged on post-operative day 8.

Case 4

An 87-year-old male with a history of abdominal aortic aneurysm status post repair, hypertension, latent TB, suspected alpha-gal allergy and recent NSTEMI with ongoing exertional angina was referred to cardiac surgery. Cardiac catheterization demonstrated severe triple vessel disease and the patient has excellent functional status so a CABG was recommended. Due to his suspected alpha-gal allergy, he was referred to an allergy specialist. Because he tolerated IV heparin during his cardiac catheterization and also had negative skin testing for heparin, no further studies were necessary prior to undergoing cardiac surgery.

The patient was treated with preoperative and perioperative steroids and diphenhydramine. He underwent a successful 3 vessel CABG and was noted to have a mild urticarial rash on his flank and limbs at the conclusion of the procedure. In the immediate postoperative period he was quite vasodilated, likely from a combination of his preoperative ACE inhibitor therapy and an allergic response, requiring significant fluid resuscitation. No albumin was given for resuscitation due to concern for alpha-gal reactivity. The vasodilatory state resolved within 24 h of surgery. He otherwise had an uneventful postoperative course.

Discussion

Limited data exists about the effect of alpha-gal allergies on cardiothoracic surgery. There is the possibility for reaction with heparin, albumin, bioprosthetic valves, and other animal derived hemostatic agents. No standardized protocol exists on how to manage these patients perioperatively in order to minimize the risk of severe IgE-mediated allergic reactions, including anaphylaxis. We treated our patients with perioperative steroids and diphenhydramine with reasonable results. This is an acceptable prophylactic strategy given the potential risk of cross reactivity and at least one case report on

demonstrated heparin reaction [7].

Interestingly, despite negative skin testing and lack of allergic reaction to IV heparin preoperatively, half of our patients had at least mild allergic reactions perioperatively. This may be a function of the much higher dose of heparin given during cardiac surgery, or may be associated with administration of albumin or other hemostatic agents. Because there is not currently a test to quantify the amount of alpha gal protein in a given medication, we can only speculate. There is no reliable test available to predict a patient's likelihood of allergic reaction. While skin testing is a relatively sensitive test, it is not specific; alpha-gal allergies are associated with variable wheal reactions to meat extract skin pricks [8,9]. This is borne out in our patient group; the patients in case 2 and case 4 had negative results to preoperative allergy testing with heparin, but demonstrated at least mild allergic responses postoperatively.

In addition to the difficulty in predicting allergic reactions for patients with known alpha-gal allergies, this allergy appears to be significantly underdiagnosed. Looking at a group of patients undergoing upper endoscopy, approximately 20%-25% of all patients evaluated were sensitized to alpha-gal [2]. One reason for late diagnosis of this allergy is that initial symptoms usually include itching and GI symptoms very similar to irritable bowel syndrome. The onset is often delayed several hours after ingestion of mammalian meat. Furthermore, patients may not have symptoms with every exposure. In most cases of allergic reaction to ingested meat, patients have consumed over 100 grams of mammalian meat [10].

The third patient in this series had a significant perioperative MI. Initially we were concerned that this was related to a technical error and that one of his bypass grafts may have gone down. His cardiac catheterization performed on postoperative day zero demonstrated thrombus formation in the LAD, distal to the LIMA anastomosis. Once he underwent balloon angioplasty, no residual abnormality was found in the distal LAD. This leads us to believe the thrombus formation and MI event were related to an IgE-mediated allergic reaction. Further support for this conclusion comes from two cases reported at our institution of patients with alpha gal food allergies who both presented with symptoms of a classic myocardial infarction. Both patients underwent cardiac catheterizations, and both had clean coronary arteries. After a thorough medical evaluation, allergic reactions were concluded to be the cause of both of these patients' myocardial infarctions as a diagnosis of exclusion.

Preoperative planning is necessary for patients who are to receive mammalian tissue prosthetic heart valves since multiple sources have found significant alpha-gal antigens on conventional glutaraldehyde-fixed prosthetic valves. This may lead to early or late allergic reactions, as well as early valve calcification and degeneration [11,12]. Animal derived hemostatic agents, like Gelfoam, may cause perioperative immune reactions as well. More research needs to be done to determine the amount of heparin necessary to incite an allergic reaction. A test allowing quantification of alpha-gal in various medications would be instrumental. This would be especially useful for heparin administration, as there are non-standardized quantities of alpha-gal in each lot of heparin.

While the four cases presented were managed differently, it is clear that with careful observation and planning, heparin can be safely used for cardiopulmonary bypass in the setting of an alpha-gal allergy. Appropriate prophylaxis with steroids and histamine receptor blockers can improve the patient's chance of a surgery without a severe IgE-mediated immune response. Preoperative allergy testing can help identify patients at risk. Further research is necessary to fully understand the role of the alpha-gal allergy in cardiac surgery.

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