



Letters

Reactivity to heparin in patients with alpha-gal allergy

A potential role for skin testing?



Galactose-alpha-1,3-galactose (alpha-gal) syndrome is an immunoglobulin (Ig)E-mediated allergy syndrome to an oligosaccharide found in nonprimate mammalian meat and mammalian-derived products.¹ Oral consumption reactions are characteristically delayed, but are immediate with parenteral administration.¹ Since the discovery of alpha-gal IgE antibodies while investigating hypersensitivity reactions to cetuximab, much attention has been paid to both theoretical risks and reported cases of hypersensitivity reactions to various medications and medical devices derived from nonprimate mammals.^{1,2} The true extent of this risk is still largely unknown.³ One medication of interest is heparin; both unfractionated heparin and low-molecular weight heparin, enoxaparin, are derived from porcine intestinal tissue. In a case of immediate hypersensitivity to heparin in a patient with a high concentration of alpha-gal-specific IgE (sIgE), we would like to draw attention to positive skin testing result to heparin products.

Patient 1 was a 62-year-old man diagnosed with alpha-gal syndrome in 2017 on the basis of history and elevated alpha-gal sIgE level. In July 2021, he was hospitalized for intravenous daptomycin through a peripherally inserted central catheter for a postsurgical toe infection. He did not receive heparin during his hospitalization. He was instructed to administer heparin 200 U flushes through his peripherally inserted central catheter on discharge. After 20 minutes from his initial heparin administration, he developed facial and oral angioedema, urticaria, and a sensation of throat closure. He took antihistamines with improvement of all symptoms over several hours and complete resolution after 3 days. Epinephrine was not administered. After 2 months, he was evaluated in our drug allergy clinic. His alpha-gal sIgE concentration at the evaluation time was more than 100 kU/L (Table 1). Although he had a negative testing result to heparin

and enoxaparin on skin prick, he had positive intradermal skin testing result to heparin at 100 U/mL and 5000 U/mL concentrations and to enoxaparin at 1 IU/mL.⁴

For the purpose of comparison, we evaluated the same heparin skin testing protocol in 3 additional patients with alpha-gal allergy without previous reaction to heparin (Table 1) and on an alpha-gal-negative control with a negative response. The alpha-gal sIgE concentration of patient 2 at evaluation was more than 100 kU/L. She had positive intradermal skin testing result to heparin at 100 U/mL and 5000 U/mL concentrations. Enoxaparin intradermal testing result was negative. The alpha-gal sIgE concentrations of patients 3 and 4 were lower, at 8.36 kU/L and 0.99 kU/L, respectively. Both patients had negative results from skin prick and intradermal testing to heparin and enoxaparin. They tolerated a subcutaneous challenge with heparin 5000 U with no symptoms during 1.5 hours of observation. On the basis of the testing results and available information, each patient received individualized recommendations regarding the future use of heparin products (Table 1).

To the best of our knowledge, we present the first case of a patient with alpha-gal allergy having a positive skin testing result to heparin products after an immediate hypersensitivity reaction to unfractionated heparin. In general, heparin hypersensitivity reactions in the setting of alpha-gal syndrome are infrequent. In 1 retrospective series of 133 patients with a documented alpha-gal allergy, a heparin product was tolerated in 56 of 57 (98.3%) hospital visits.⁵ A single patient experienced a self-limited reaction to the second dose of subcutaneous unfractionated heparin; he had one of the cohort's highest alpha-gal sIgE concentrations (24.20 kU/L).⁵ In another retrospective study of 8819 cardiac surgery patients, 17 patients were found to have elevated alpha-gal sIgE level preoperatively, of which 4 of 17 patients (23.5%) had a severe allergic reaction to heparin.⁶ Those patients who reacted to heparin were found to have higher alpha-gal sIgE concentrations (> 75 kU/L) than those who did not.⁶ There may be a higher risk of a hypersensitivity reaction with systemic heparinization, owing to large doses of intravenous heparin required for cardiac surgery compared with much lower doses of subcutaneous administration of thromboprophylaxis.⁶

A uniform testing strategy for heparin allergy in patients with alpha-gal allergy does not exist. A previous case report suggested using heparin skin testing and challenge as diagnostic options.⁷ We provide evidence that heparin skin testing may be of value to complement alpha-gal sIgE concentrations and could be studied at the point of care. Our findings corroborate those of other studies, suggesting that patients with higher alpha-gal sIgE concentrations may be more likely to react to heparin.⁵⁻⁷ We hypothesize

Disclosures: Dr Phillips reports receiving grants and funding from the National Institutes of Health (R01HG010863, R01AI152183, U01AI154659, R13AR078623, UAI109565) and from the National Health and Medical Research Council of Australia. The remaining authors have no conflicts of interest to report.

Funding: Dr Stone received funding from the Agency for Healthcare Research and Quality and the Patient-Centered Outcomes Research Institute 1K12HS026395-0 and received an American Academy of Allergy, Asthma & Immunology Foundation Faculty Development Award. Dr Phillips reports receiving grants and funding from the National Institutes of Health (R01HG010863, R01AI152183, U01AI154659, R13AR078623, UAI109565) and from the National Health and Medical Research Council of Australia; receiving royalties from UpToDate; receiving consulting fees from Janssen, Vertex, Biocryst, Regeneron, and Verve; serving as a co-director of IID Pty Ltd that holds a patent for HLA-B*57:01 testing for abacavir hypersensitivity; and having a patent pending for Detection of Human Leukocyte Antigen-A*32:01 in connection with Diagnosing Drug Reaction with Eosinophilia and Systemic Symptoms without any financial remuneration and not directly related to the submitted work. The funders played no role in any aspect of this manuscript.

This study was done under institutional review board–approved protocols from Vanderbilt University (IRB #161455).

Table 1
Patient Demographics and History, Serum IgE Concentrations, and Skin Testing Results

History and Testing	Patient 1	Patient 2	Patient 3	Patient 4
Age	62 y	70 y	67 y	66 y
Sex	Male	Female	Female	Female
Race	White	White	White	White
Ethnicity	Non-Hispanic	Non-Hispanic	Non-Hispanic	Non-Hispanic
Year of alpha-gal syndrome diagnosis	2017	2019	2014	2019
Reaction history to alpha-gal	Delayed urticaria, facial angioedema, nausea, and gastrointestinal upset to beef or pork	Delayed anaphylactic reaction to beef	Delayed urticaria and shortness of breath to mammalian meat	Delayed anaphylactic reaction to beef
Date of last known reaction to alpha-gal	March 2019	October 2019	2014	January 2020
Date of last known tick bite	Unknown	Summer 2021	Unknown	March 2020
Indication for heparin testing	Immediate hypersensitivity reaction to heparin flush in July 2021	Recent hospitalization in which heparin was not administered, evaluation to determine whether heparin could be used	Recent diagnosis of cancer and at risk for thrombosis, evaluation to determine whether heparin could be used	Recent systemic thrombosis, evaluation to determine whether heparin could be used
Date of evaluation in drug allergy clinic	September 23, 2021	January 23, 2022	September 9, 2021	June 17, 2021
IgE concentrations at time of heparin skin testing				
Date (mo/y)	September 2021	November 2021	September 2021	June 2021
Alpha-gal IgE (kU/L)	>100.00	>100.00	8.36	0.99
Beef IgE (kU/L)	65.00	36.00	5.39	0.65
Lamb IgE (kU/L)	19.20	7.33	3.52	0.18
Pork IgE (kU/L)	28.30	12.50	3.05	0.35
Skin prick testing results ^a				
Heparin 1 U/mL	—	—	—	—
Heparin 100 U/mL	—	—	—	—
Heparin 5000 U/mL	—	—	—	—
Enoxaparin 0.1 IU/mL	—	—	—	—
Enoxaparin 1 IU/mL	—	—	—	—
Intradermal skin testing results ^a				
Heparin 1 U/mL	—	—	—	—
Heparin 100 U/mL	+	+	—	—
Heparin 5000 U/mL	+	+	—	—
Enoxaparin 0.1 IU/mL	—	—	—	—
Enoxaparin 1 IU/mL	+	—	—	—
Subcutaneous challenge with heparin 5000 U	Did not perform	Did not perform	Passed	Passed
Recommendations given to patient	Avoid all heparin products.	Avoid all heparin products.	Safe to receive heparin products. ^b	Safe to receive heparin products. ^b

Abbreviations: +, positive; —, negative; IgE, immunoglobulin E.

^aSkin test protocol has been used in 8 patients in total (5 patients and 3 healthy controls) at our institution, with only 2 of them having signs of a positive test result thus far.

^bPatients 3 and 4 were given the recommendations that it is safe to receive heparin products at the end of their evaluation. Additional clarification for these recommendations suggests that it is safe to receive subcutaneous heparin products less than or equal to 5000 U, but should exercise caution with intravenous administration and higher doses, such as more than 5000 U, of subcutaneous heparin. Premedication with antihistamines may be advisable.

that the same might also be true for demonstrating positive heparin skin testing result. A notable difference between patient 1 and patient 2, despite similar alpha-gal sIgE concentrations of more than 100 kU/mL, is opposing skin testing results to enoxaparin. It has been speculated that low-molecular weight heparin may have a different risk profile for alpha-gal.⁶ In a study by Nwamara et al,⁵ 0 of 22 patients (0%) reacted to enoxaparin compared with 1 of 39 patients (2.6%) who reacted to unfractionated heparin. One could hypothesize that this could be because of differences in alpha-gal content related to molecular weight and manufacturing processes.

Patient 1 had an alpha-gal sIgE concentration more than 100 kU/L and reacted immediately to heparin given intravenously. However, his hypersensitivity reaction to heparin did not require epinephrine or emergent medical evaluation. Other reports do not provide a pattern in reaction severity on the basis of serum alpha-gal sIgE concentrations.^{5–7} On the basis of literature, patients with alpha-gal allergy can have systemic reactions to heparin,⁶ and therefore, evaluation and management strategies are needed. There is a possibility that skin testing may yield false positives or negatives, which will need to be established with larger series.⁸ Therefore, clinicians must exercise caution with skin testing because the sensitivity and

specificity remain unknown at this time. Quantifying the amount of alpha-gal contained in drugs and vaccines with mammalian ingredients⁹ and understanding the interaction with route of administration in causing reactions are crucial future directions.

In conclusion, given the frequency of heparin use, allergy clinicians should be aware of the possibility of hypersensitivity reactions with alpha-gal syndrome and perform a thoughtful evaluation. Based on our experience, we hypothesize that skin testing with heparin may be of value as a discriminator between attempting a challenge vs future desensitization when heparin is needed, particularly in those with high concentrations of alpha-gal sIgE. This is important because alpha-gal sIgE concentration alone may not predict the reaction risk and severity. Additional research is needed to determine the prevalence of heparin allergy in the setting of the alpha-gal syndrome, the role of skin testing, and the concentration of alpha-gal sIgE that qualifies as higher risk.

Acknowledgments

The authors acknowledge Brandi Jacobs, PharmD; Sara Bluestein, MD; and Pragya Shrestha, MD; for their assistance in testing the patients in this report.

Grace Koo, MD*
 Jessica Plager, MD*
 John M. Fahrenholz, MD*
 Elizabeth Phillips, MD^{†,‡,§}
 Cosby Stone Jr, MD, MPH*

* Division of Allergy
 Pulmonary and Critical Care Medicine
 Department of Medicine
 Vanderbilt University Medical Center
 Nashville, Tennessee

[†] Division of Infectious Diseases
 Department of Medicine
 Vanderbilt University Medical Center
 Nashville, Tennessee

[‡] Department of Pathology
 Microbiology
 and Immunology
 Vanderbilt University School of Medicine
 Nashville, Tennessee

[§] Institute for Immunology & Infectious Diseases
 Murdoch University
 Murdoch, Western Australia
cosby.a.stone@vumc.org

References

1. Platts-Mills TAE, Li RC, Keshavarz B, Smith AR, Wilson JM. Diagnosis and management of patients with the α -gal syndrome. *J Allergy Clin Immunol Pract.* 2020;8(1):15–23. e1.
2. Commins SP. Diagnosis & management of alpha-gal syndrome: lessons from 2,500 patients. *Expert Rev Clin Immunol.* 2020;16(7):667–677.
3. Caballero ML, Krantz MS, Quirce S, Phillips EJ, Stone Jr. CA. Hidden dangers: recognizing excipients as potential causes of drug and vaccine hypersensitivity reactions. *J Allergy Clin Immunol Pract.* 2021;9(8):2968–2982.
4. Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs. *J Allergy Clin Immunol Pract.* 2020;8(9S):S16–S116.
5. Nwamara U, Kaplan MC, Mason N, Ingemi AL. A retrospective evaluation of heparin product reactions in patients with alpha-gal allergies. *Ticks Tick Borne Dis.* 2022;13(1):101869.
6. Hawkins RB, Wilson JM, Mehaffey JH, Platts-Mills TAE, Ailawadi G. Safety of intravenous heparin for cardiac surgery in patients with alpha-gal syndrome. *Ann Thorac Surg.* 2021;111(6):1991–1997.
7. Mawhirt SL, Banta E. Successful intravenous heparin administration during coronary revascularization surgery in a patient with alpha-gal anaphylaxis history. *Ann Allergy Asthma Immunol.* 2019;123(4):399–401.
8. Stone Jr CA, Choudhary S, Patterson MF, Rukasin CRF, Coleman DT, Phillips EJ, et al. Tolerance of porcine pancreatic enzymes despite positive skin testing in alpha-gal allergy. *J Allergy Clin Immunol Pract.* 2020;8(5):1728–1732. e1.
9. Campbell E, Peebles S, Stone Jr CA, Zhang J, Hadadianpour A, Doyle J, et al. Evaluation of alpha gal in vaccines and medications using a human monoclonal IgE antibody. *J Allergy Clin Immunol.* 2021;147(2):AB7.

Transient acquired donor peanut allergy presenting as life-threatening anaphylaxis following lung transplantation



Transient acquired donor immunoglobulin (Ig)E-mediated food allergy after solid organ transplantation (SOT) has been described in a few case reports and in 1 systematic review. Theories regarding mechanism range from passive transfer of allergen-specific IgE through sensitized donor mast cells,¹ to transfer of B lymphocytes producing allergen-specific IgE or allergen-specific Th2 lymphocytes into the circulation at the time of transplantation.²

We describe a case of allergy transfer in a recipient of lung retransplantation who has immunosuppression. Informed consent was obtained.

A 50-year-old man, with no history of allergic disease, underwent a second lung transplant (LTx) for end-stage chronic lung allograft dysfunction. Immunosuppression included induction basilixumab and methylprednisolone tapering to maintenance prednisolone, mycophenolate mofetil, and tacrolimus by discharge at day 14. The donor lungs were from an adolescent aged 16 years with atopy, who died after a pulseless electrical activity cardiac arrest attributed to asthma on the background of known asthma and peanut allergy with previous anaphylaxis. Donor sensitization to peanut was confirmed retrospectively with elevated serum peanut-specific IgE 93.3 kU/L (range, 0–0.34 kU/L) immediately before transplantation and a positive skin prick test result to peanut 25 mm (range, 0–3 mm) performed 2.5 years before the transplant.

Sixteen days after LTx, the recipient became acutely dyspneic within 5 minutes of ingesting peanut. On ambulance arrival, he was hypoxic, with wheeze and oxygen saturations of 56% on room air and tachycardic to 133 beats per minute, but normotensive, with no cutaneous manifestations of IgE-mediated allergy. Initial management included 0.5 mg intramuscular adrenaline, intravenous fluid

resuscitation, and nebulized bronchodilators with initial stabilization. On route to the hospital, 56 minutes after the initial dose of intramuscular adrenaline, he developed rebound anaphylaxis with hypotension to 80/40 mm Hg, altered conscious state, refractory hypoxia, and abdominal pain. He was treated with an intravenous bolus of 5 μ g of adrenaline followed by an infusion at 5 μ g/min. Adjuvant treatments on arrival to the emergency department included adrenaline infusion dose escalation, intravenous hydrocortisone, and H1 antagonists. He was admitted to the intensive care unit, where his symptoms continued to improve, enabling weaning and cessation of the adrenaline infusion over 12 hours. Routine pathology tests and chest x-ray examination did not suggest an alternative cause for the clinical presentation. The reaction was associated with a dynamic increase in serum tryptase to 10 μ g/L 2 hours after symptom onset, returning to 3.1 μ g/L 24 hours later. A baseline serum tryptase added retrospectively to pretransplant blood samples was 4.3 μ g/L.

The recipient retrospectively recalled an episode of acute wheeze after the ingestion of peanuts the week preceding the reaction; the symptom responded to inhaled short-acting bronchodilators. Before his second lung transplant, he had no history of allergic disease and tolerated an unrestricted diet incorporating peanuts and peanut-containing products frequently. Peanut-specific IgE was undetectable in serum samples taken in the weeks before his second transplant, confirming no evidence of previous sensitization. Skin prick tests and serum specific IgE immunoassay to peanut (Table 1) performed after his second transplant were transiently but significantly elevated.

After the reaction, the recipient practiced strict peanut avoidance with close monitoring of markers of peanut sensitization. On re-examination, he was found to have negative skin test results to peanut and undetectable serum peanut-specific IgE. He proceeded to a supervised graded oral challenge to peanut 18 months after the transplant; the challenge was negative to a cumulative dose of 4