Delayed Anaphylaxis to Mammalian Meat Following Tick Exposure and Its Impact on Anesthetic Management for Cardiac Surgery: A Case Report

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Hypersensitivity reactions to mammalian meat following tick exposure are increasing in prevalence and provide a unique challenge to anesthesiologists. The reactions, including anaphylaxis, are delayed and therefore may not be easily recognized and treated. The risk is especially high in cardiac surgery, where several potential triggers, including biological valves as well as heparin, are used frequently. In the presence of such hypersensitivity, prophylactic measures including preoperative testing and pharmacologic prophylaxis may be useful in modulating the immune response such that triggering agents may be used relatively safely. We present 3 patients with previous sensitization to meat protein following a tick bite with known allergic reactions to mammalian meat who presented for cardiac surgery involving exposure to potential allergens and discuss the perioperative management including possible prevention. (A&A Case Reports. 2017;XXX:00–00.)

Because of the wide range of medications and other products given perioperatively, hypersensitivities are particularly important to the anesthesiologist. Anaphylaxis following mammalian meat exposure, first diagnosed in 2006 and described in 2009, presents a specific challenge for cardiac surgery because many products, including valves, as well as heparin provide, potential triggers.[1,2] Moreover, secondary to the delay in onset of 3 to 6 hours, initial signs of anaphylaxis may occur in the intensive care unit or postoperative unit, where the causative relationship may not be recognized immediately and immediate treatment may be more challenging. Unfortunately, heparin alternatives are associated with significant risks of their own, including significant bleeding. In the presence of such hypersensitivity, prophylactic measures may be useful in attenuating anaphylactic responses such that triggering agents may be used relatively safely. All patients have provided written consent for publication of this manuscript.

CASE 1

A 73-year-old man with severe aortic stenosis and paroxysmal atrial fibrillation presented for aortic valve replacement using a Magna Ease® tissue valve (Edwards Lifesciences Corp., Irvine, CA) and left atrial appendage ligation. His medical history was significant for anaphylactic reaction to mammalian meat following a tick bite.

Intravenous (IV) heparin was administered for initiation of cardiopulmonary bypass following prophylactic IV dosing of dexamethasone 10 mg IV and diphenhydramine 50 mg IV. The surgical procedure and anesthetic were uncomplicated until the end of the procedure, when the patient was noted to have an urticarial rash. Approximately 4 minutes later, the patient had declining oxygen saturations and increased peak airway pressures with wheezing. Epinephrine infusion was increased from 4 μg/min to 12 μg/min, and the patient was given additional dexamethasone 10 mg IV. The patient's hypotension and hypoxia continued requiring epinephrine boluses. Additional diphenhydramine and albuterol were administered without resolution of symptoms. Approximately 30 minutes following the initial onset of symptoms, famotidine 20 mg IV was administered with resolution of hypotension, hypoxia, and rash within 10 minutes.

CASE 2

A 43-year-old woman with a history of tick-associated meat allergy presented for subclavian artery repair and epicardial lead placement on cardiopulmonary bypass. The patient received hydrocortisone 100 mg, famotidine 20 mg, and diphenhydramine 50 mg intravenously before incision. IV heparin was administered before the initiation of cardiopulmonary bypass. The surgery and anesthetic proceeded without incident. A very mild urticarial rash without any other symptoms of allergic reaction was noted postoperatively in the cardiac intensive care unit.

CASE 3

A 67-year-old woman with severe mitral regurgitation and nonischemic cardiomyopathy (ejection fraction 35%–40%) presented for minimally invasive mitral valve repair. She reported a 17-year history of allergies to mammalian meat following approximately 500 tick bites. Her symptoms initially were generalized urticaria but developed after 2 months to include several incidences of anaphylaxis with meat exposure. She had been asymptomatic for 3 years with meat avoidance. Allergy and immunology services were consulted and recommended a heparin challenge the evening before her procedure to be performed with heparin from the same lot that would be used for the procedure. Her heparin challenge was negative, and she was given

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Accepted for publication October 20, 2016.

Funding: None.

The authors declare no conflicts of interest.

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DOI: 10.1213/XAA.0000000000000457

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IV heparin from the same lot for initiation of cardiopulmonary bypass the next day. Despite a negative heparin challenge, she received diphenhydramine, famotidine, and hydrocortisone intravenously before heparin administration. She experienced no intraoperative or postoperative hypersensitivity symptoms.

DISCUSSION

Hypersensitivity reactions occur when the immune system responds to soluble antigens. Delayed anaphylaxis to red meat is characterized by late-onset urticaria or anaphylaxis along with a history of pruritic tick bite, exposure to red meat or a product derived from red meat 3 to 5 hours before the reaction, and a lack of an alternative immediate cause.[1] Tick-associated adult onset anaphylaxis results from pre-existing IgE antibodies to mammalian galactose-α-1,3-galactose (α-gal) that can form after exposure to a tick bite. These IgE antibodies are formed when exposure to tick antigens produces an IgE response that cross-reacts with α-gal.[2,3] Humans lack a functional α-1,3-galactosyltransferase gene, and a large portion of humans create IgA, IgG, and IgM antibodies against the α-gal protein in response to immune stimulation by enteric bacteria.[4] Interestingly, the route of initial exposure to the antigen is through the skin, whereas symptoms can occur following oral or IV administration.

Unlike other hypersensitivity IgE responses that occur almost immediately, these particular antibodies are associated with a delayed form of hypersensitivity or anaphylaxis occurring most frequently 3 to 6 hours after exposure to a mammalian (nonprimate or human) substance, including meat from beef, pork, and lamb as well as, rarely, milk and cheese.[2,5] Symptoms include nausea, diarrhea, urticarial rash, and most frequently itching. These symptoms never occur <2 hours following exposure. In addition, reactions often are unpredictable and may not occur after every exposure to mammalian meat. Patients do not react to nonmammalian meats, including turkey, chicken, and fish, because nonmammalian tissues do not contain α-gal.[6]

The diagnosis of tick-associated adult onset anaphylaxis is particularly difficult because patients display only weak (2–4 mm) or negative wheal responses to skin prick tests with beef, pork, or lamb extract tests. The same patients, however, will react positively to intradermal testing with commercial meat extracts and skin prick tests using fresh meat extracts.[7,8] Titers may decrease over time if tick exposure is avoided; however, this is unpredictable, and the symptoms may not be lessened with decreased titers. Meanwhile, repeated exposure to tick bites appears to increase the immune response to α-gal.[2]

The majority of cases have presented in the area, including Virginia, North Carolina, Tennessee, Arkansas, Georgia, and Missouri, although patients in surrounding states Europe, Australia, Africa, and Asia also have been affected.[3,9] Allergy to α-gal is now the most common cause of anaphylaxis in adult patients in central Virginia. Cases in the United States are associated with the lone star tick (*Amblyomma americanum*), whereas cases in other countries seem to be because of exposure to other tick species including *Ixodes holocyclus* in Australia and *Ixodes ricinus* in Europe.[2] The recent increase in the deer population and thus increase in the number of ticks is thought to be the cause of the sudden increase in cases of tick-associated anaphylaxis in the United States and abroad. Areas with climates that do not support either ticks or their carriers have tested negative for IgE antibodies to α-gal.[5,9]

Heparin poses a theoretical risk because heparin is sourced from bovine lung and porcine intestinal mucosa. Although α-gal is not one of the oligosaccharides present in heparin, there is a lot-to-lot variability of impurities and a potential contamination with alpha-gal is possible.[10] Avoiding the use of heparin during cardiopulmonary bypass or for major vascular surgery is particularly challenging because heparin alternatives can be difficult to manage and often are less familiar to clinicians. Although the effect of heparin is reversed quite easily following cardiopulmonary bypass with protamine, heparin alternatives, including bivalarudin and argatroban, are not reversible. The anticoagulant effects of these medications must be allowed to diminish over time, which can be associated with significant bleeding and an increase in transfusion requirements.

Biological valves can be made from either bovine or porcine tissue. Initially, valves were treated with glutaraldehyde to sterilize the tissue and to reduce antigenic responses; however, these valves may still trigger an antibody response to α-gal.[9,10] The process of decellularization (mechanical and/or chemical) disrupts the cell membranes and removes most cellular and nuclear components when leaving the extracellular matrix (scaffold) intact.[10,11] Because of the lack of α-gal release from decellularized valves, a decreased immune response in the recipient is observed—leading to a longer durability of these valves as compared with those treated with glutaraldehyde.[12] When possible, decellularized valves should be used for patients with known α-gal response. In addition to valve and tissue patch products, bovine serum albumin also can lead to a reaction in susceptible patients.[2]

Steroids and histamine receptor blockers have been used successfully to treat or prevent hypersensitivity reactions, including allergies to radiocontrast dye.[13] On the basis of our experience, prophylaxis with steroids and both histamine 1 and 2 receptor blockers appear effective in attenuating the response seen after α-gal exposure to the point where heparin and other products derived from mammalian tissue may be used safely. When one or more components of the prophylactic regimen are excluded, however, life-threatening anaphylaxis may ensue. Treatment with epinephrine, steroids, histamine blockers, and supportive care should be immediately delivered if unexpected increases in airway pressures, hypotension, urticaria, and other symptoms of anaphylaxis occur 4 to 6 hours after heparin or other mammalian tissue exposure.

In addition, a heparin challenge with the same heparin lot to be used for anticoagulation may be considered before cardiac surgery, given the possibility of hypersensitivity from heparin contaminants. Because of the possibility of anaphylaxis and the delayed onset, this should be done in an inpatient setting to ensure prompt treatment should a reaction occur. If the heparin challenge is negative, the same lot should be able to be safely used for anticoagulation, although additional prophylactic medications may still be given to further ensure safe use.

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DISCLOSURES

Name: Amanda M. Kleiman, MD.
Contribution: This author provided intraoperative care, and helped design and write the manuscript.
Name: Keith E. Littlewood, MD.
Contribution: This author helped design and write the manuscript.
Name: Danja S. Groves, MD, PhD.
Contribution: This author helped design and conduct the study.
This manuscript was handled by: Raymond C. Roy, MD.

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