



Demystifying α -gal syndrome: identification and risk management in the perioperative setting

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Purpose of review

α -Gal syndrome is among a vexing perioperative consideration for anesthesiologists. Commonly referred to as 'red meat allergy', α -Gal syndrome is precipitated by a lone star tick bite resulting in the formation of immunoglobulin E (IgE) antibodies against the tick salivary glycoproteins and noncatarrhine mammalian tissue.

Recent findings

Up to 20% of the population in the southeastern United States may test positive for IgE antibodies to α -Gal. Increasingly, recognition of α -Gal syndrome as an immune response to red meat consumption and certain drugs, many of which may be administered within the perioperative period, has led to greater awareness of the insidious nature of its presentation – from mild urticaria and gastrointestinal symptoms to severe anaphylaxis.

Summary

With the increasing prevalence and identification of α -Gal syndrome, a safe and tailored perioperative process is needed to integrate a pathway that involves multidisciplinary communication, robust information sharing platform, and a structured peri-procedure management.

Keywords

α -Gal, anaphylaxis, gelatin, red meat, tryptase

INTRODUCTION

The clinical practice of anesthesia requires diligent preparation in order to avoid *predictable* crises, even though it is the *unexpected* problems that usually prove most vexing. One such diagnosis is α -Gal syndrome, a condition that can have life-threatening consequences in the perioperative setting. α -Gal syndrome (mammalian meat allergy) is an immunoglobulin E (IgE)-mediated allergic reaction to galactose- α -1,3-galactose (α -Gal), which is found in the glycoproteins and glycolipids of most mammals, with the exception of humans and primates [1^a,2^a,3,4^a,5,7]. α -Gal syndrome presents with delayed-onset anaphylactic reactions after ingesting α -Gal-containing foods, generally beginning 2–6 h after consuming red meat such as: beef, bison, pork, lamb, and venison [5,7]. In the United States, IgE against α -Gal typically follows a tick bite, generally from the lone star tick *Amblyomma Americanum*, which is most prevalent in the southeastern United States [1^a]. The tick bite leads to the production of IgE against α -Gal, but does not trigger an

allergic reaction [1^a,3]. The high levels of IgE antibodies arm mast cells by binding to high-affinity receptors for IgE; such mast cells can then be activated when exposed to a carrier antigen containing at least two α -Gal moieties that aggregate IgE on the mast cell surface. When these individuals consume mammalian meat, they exhibit a delayed anaphylactic reaction, presumably due to the time it takes to transfer α -Gal from monovalent animal antigen carriers to putative multivalent carriers in humans. Clinical manifestations range in severity from

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KEY POINTS

- α -Gal syndrome is an under-recognized allergy condition in the perioperative setting, where it presents unique challenges.
- α -Gal syndrome occurs in those with IgE-antigalactose- α -1,3-galactose (α -Gal) and most commonly presents as delayed-onset anaphylaxis, 2–6 h after ingestion of mammalian meats.
- Sensitization is associated with lone star tick bites, although anaphylaxis is not directly triggered by tick bites.
- Immediate reactions can occur with exposure to multivalent α -Gal-containing proteins, which can be seen with the administration of gelatin-containing vaccines and medications, leading to activation of mast cells by aggregating IgE anti- α -Gal on the cell surface.
- Given the serious implications of α -Gal allergy, increasing knowledge and awareness of the α -Gal syndrome among anesthesiologists is paramount to safe and tailored perioperative care.

localized hives or angioedema, to severe hypotensive anaphylaxis [1[■],2[■],3,4[■],6,8].

This syndrome was first identified in the mid-2000s, when cancer patients in the southeastern United States exhibited rapid-onset anaphylactic reactions during their first exposure to cetuximab, an IgG monoclonal chimeric antibody used for the treatment of solid tumors such as head, neck, and colon cancers [6,8]. After further examination, it was discovered that the IgE anti- α -Gal antibodies were in the pretreatment sera of these patients. Additional research has shown that immediate anaphylaxis was due to IgE anti-cetuximab antibodies specific for the α -Gal oligosaccharide, made by the mouse hybridoma used to produce cetuximab, and placed on the Fab region of the two IgG heavy chains of cetuximab [8]. Thus, in the perioperative setting, exposure to animal proteins in medications or devices (see peri-procedure implications below) can cause rapid onset of anaphylaxis, which can be precisely diagnosed if the acute serum tryptase level (sAT), obtained 30 min to 2 h after clinical onset is significantly higher than the baseline level (sBT) as per the algorithm: $[sAT > 1.2 \times sBT + 2]$ [12–18]. Of note, the sBT is measured by serum collected before onset of the reaction or at least 24 h after all signs and symptoms have resolved.

RELEVANT IMPLICATIONS

With the emergence of the COVID-19 pandemic and social distancing, outdoor activities have

increased in popularity. The pandemic has led to the number of available and safe activities to become limited, although outdoor activities have been on the rise. State parks in North Carolina have seen increased numbers in visitation since the start of the pandemic [19]. However, the reporting of tick-borne illnesses across North Carolina has actually slowed down [19]. One possible explanation for this could be that because healthcare professionals have been bombarded with taking care of critically ill COVID-19 patients, the reporting of α -Gal syndrome has been under-recognized. Nonetheless, the prevalence of α -Gal syndrome, as well as other tick-borne illnesses, will likely increase over the next few months, making the recognition of this condition increasingly relevant.

PERI-PROCEDURE IMPLICATIONS

α -Gal syndrome presents a vexing medical challenge because α -Gal conjugates are present in many animal-derived medications and surgical products, including: biologics, biologic mesh, surgical powder, pancreatic enzyme replacement, and heart valves [1[■],3]. α -Gal conjugates can be present as inactive ingredients or impurities in medications or animal-derived devices such as glycerin, gelatin, and stearate, which are available from many perioperative medication formularies [3]. Acetaminophen tablets are often administered in a preoperative setting and contain the inactive ingredient magnesium stearate [1[■]]. Animal-derived gelatin is present in medical products such as Zostavax and yellow fever vaccines, plasma expanders, and capsules [1[■]]. Animal-derived products, such as heparin and heart valves, are also a concern for those with α -Gal syndrome [1[■]]; the rapid degeneration of mammalian valves and anaphylaxis has been described in affected patients [9–11].

Failing to recognize underlying conditions that might affect surgical patients in the perioperative setting could result in delay or postponement of the surgery or adverse event. This potential situation can arise when managing a patient with α -Gal syndrome, as the content of alpha-Gal-containing inactive ingredients in the various medications used during the perioperative period is variable. The α -Gal composition of different lots of a drug from the same manufacturer or from the same drug made by different manufacturers can vary, which makes it difficult to predict the outcome [3]. Often the source of the inactive ingredient(s), whether it is plant- or animal-derived, is not explicitly stated in the manufacturer's provided package insert, and this information can only be obtained via direct contact with the manufacturer. This process can take up to several

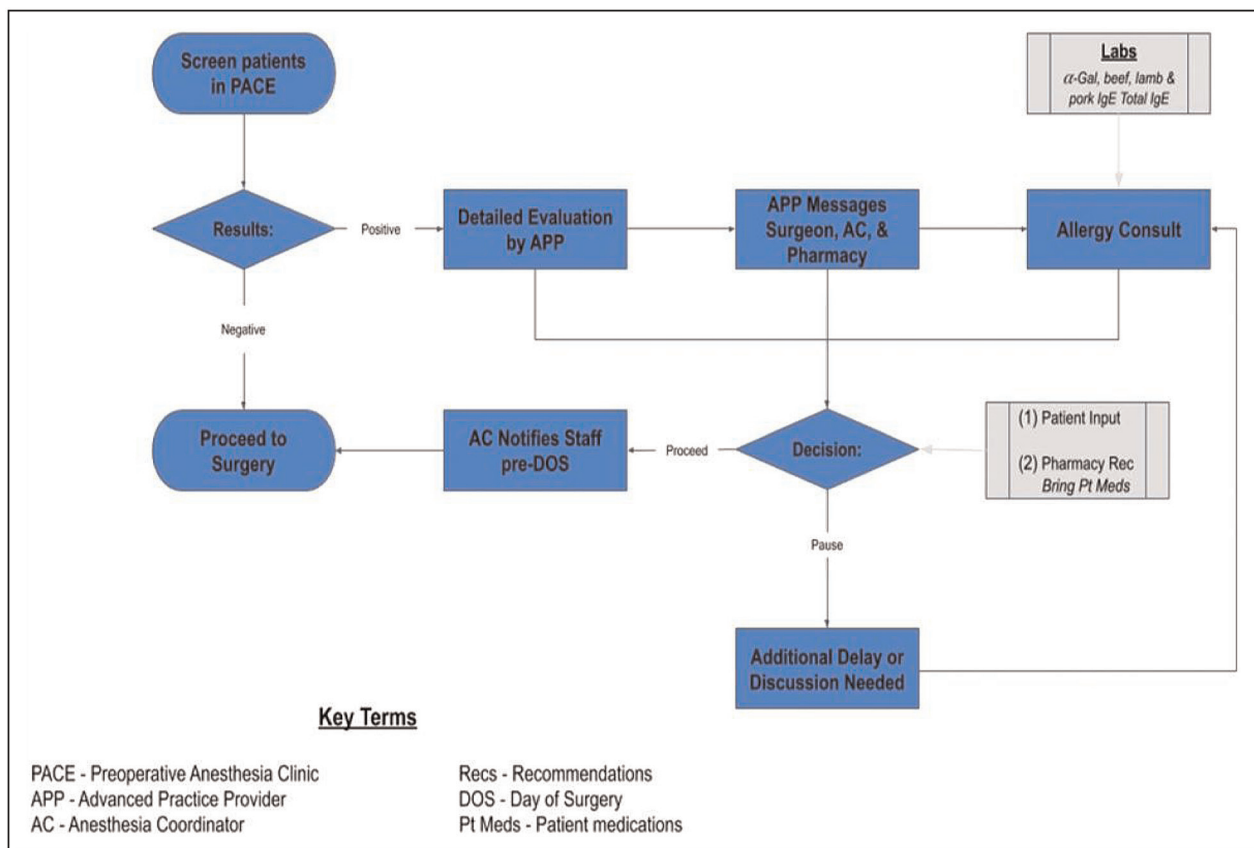


FIGURE 1. Preoperative process for α -Gal syndrome.

days, which ultimately delays appropriate patient care.

MANAGEMENT

Increasing knowledge about α -Gal syndrome promotes a safe and tailored perioperative care. As an academic institution in a region where as many as 20% of our patients may test positive for IgE antibodies to α -Gal [3,4²²,8], our health system has begun integrating an interdisciplinary approach to identifying at-risk patients (Fig. 1). In our Preoperative Anesthesia Clinic, nurses now systematically screen patients with the following questions: Do you have a history of a red meat allergy, including to pork, beef or lamb? Have you had a previous allergic reaction to cetuximab or the yellow fever or Zostavax vaccine? (Table 1) If the screen is positive, further evaluation by an allergy/immunology specialist is initiated. Detailed assessment then involves further questioning to determine whether the clinical history is consistent with a mast cell activation event, delayed allergic reactions to red meats, and immediate allergic reactions to gelatin containing foods, such as gummy bears or

marshmallows. Patients are questioned about previous testing and evaluation by an allergist for α -Gal allergy. With the suspicion of an α -Gal allergy, appropriate blood testing is ordered, including: IgE levels against α -Gal, beef, lamb and pork, as well as a total IgE level. Along with a positive IgE test to mammalian animals from at least two species, α -Gal IgE levels above 2 IU/mL or a ratio of α -Gal to total IgE >2%, increases the likelihood of anaphylactic reactions. Levels less than these thresholds reduce, but do not eliminate, such a reaction [1⁹]. Once identified, α -Gal allergy is noted in the patient's chart as it becomes essential knowledge for future

Table 1. Preprocedure screening and list of symptoms for α -Gal syndrome

Screening for α -Gal
History of a red meat allergy (pork, beef and lamb)?
Previous allergic reaction to Cetuximab or the yellow fever or Zostavax vaccine?
Symptoms (onset 2–6 h after ingestion of red meat)
itching, gastrointestinal symptoms (nausea, diarrhea, indigestion), urticaria, angioedema, anaphylaxis

surgical and medical care. The surgeon, allergist, anesthesiology coordinator, and perioperative pharmacists must collaborate in order to proactively devise a plan for which therapeutics can be safely administered to these at-risk patients in the perioperative setting.

Prior to the day of surgery, accurate lists of patients' home medications are obtained by pharmacy. Patients are then instructed to bring their home medications, excluding controlled substances, on the day of surgery. This process ensures patients are administered tolerable medications and significantly reduces the workload for pharmacy staff if the patient is admitted. Perioperative medications are reviewed by pharmacy, in consult with allergy, to determine safety prior to administration. Currently, by mouth medications are excluded from this review unless the patient has a history of an anaphylactic reaction to oral medications, or at the request of the physician. Pharmacy maintains a list of intravenous medications safe to administer to α -Gal allergy patients. At our institution, an ongoing discussion revolves around the safety of various surgical supplies and devices. The involvement of central supply stakeholders will be pertinent for future success.

Identifying such risk preoperatively does have its limitations. The α -Gal allergy may be missed in surgical patients who bypass the ambulatory presurgery clinic, particularly those requiring time sensitive surgeries from the ED or inpatient wards. Moreover, limited awareness of those who screen patients, or patients that do not provide an accurate history, may result in missing such cases. Some clinicians may perceive an α -Gal allergy as a standard food allergy and overlook its perioperative significance [4[■]]. Even when correctly identified, the lack of tools and support may prevent the proper documentation and communication of this syndrome within a patient's record [4[■]].

CONCLUSION

Recognition of α -Gal syndrome has been on the rise, and its clinical significance is important for the safety of patients. Physicians and the clinical team should have a high index of suspicion when they encounter patients who describe experiencing delayed anaphylactic reactions following the consumption of red meats or have had previous reactions to specific drugs and vaccines that contain gelatin or other animal meat proteins. In the perioperative setting, a thorough history is pivotal. An institution-wide support network facilitates the development of protocols involving a multidisciplinary approach to the identification of risk, as well

as the communication of vital information to front-line providers. The preoperative identification of an α -Gal allergy, allows medical staff to adapt the care in the perioperative setting, better protecting their patients.

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Conflicts of interest

L.S.: VCU collects royalties from Thermo Fisher for the tryptase assay that are shared with L.S., its inventor. The remaining authors have no conflicts of interest.

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