Alpha-Gal Syndrome in Ophthalmology and Medicine

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Introduction

Galactose-alpha-1,3-galactose (alpha-gal) is a carbohydrate moiety abundantly expressed in the cells and tissues of all mammalian species except primates. Structurally similar to the B blood group antigen, alpha-gal has historically been recognized as an antigenic cause of unsuccessful xenotransplantation.[1] As humans are unable to synthesize alpha-gal, they naturally produce IgM and IgG antibodies against the oligosaccharide, which can lead to hyperacute transplant rejection.[1] In recent years, alpha-gal has been implicated as a trigger for delayed anaphylaxis to a wide range of mammalian meats (often called "red meat"), organ meats, and animal products such as gelatin and dairy.[2,3] Alpha-gal has also been linked to severe hypersensitivity reactions to cetuximab in the southeastern United States.[4] Serum studies from affected patients revealed preformed IgE antibodies to alpha-gal, and the condition was subsequently named "alpha-gal syndrome."[5] The purpose of this work is to briefly describe the discovery and clinical manifestations of the condition and the implications for ophthalmic surgery.

History

Cetuximab

When the monoclonal antibody cetuximab was approved for cancer treatment in 2004, it soon became apparent that allergic reactions were occurring in relation to the medication throughout major clinics in the

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southeastern United States.[6] These patients were experiencing immediate hypersensitivity reactions upon first infusion of the medication, with symptoms developing within 20 minutes of infusion that were severe and the cause of several fatalities.[7] Serum studies from these patients demonstrated IgE antibodies specific to alpha-gal on the heavy chain antigen-binding fragment (Fab) portion of cetuximab.[8]

In 2007, it was reported that these hypersensitivity reactions were only occurring in 1.2% of the general population compared with 22% of patients in Tennessee and North Carolina.[6] In 2008, a study revealed that 20% of healthy control subjects from Tennessee reported IgE antibodies to cetuximab.[4] Finally, in 2011, Commins et al[9] reported IgE to alpha-gal in 18% to 22% of patients in random populations from Virginia, Tennessee, and North Carolina. These data suggested a relatively higher incidence of alpha-gal allergy in the southeastern region of the United States, with sensitization occurring geographically.

Meat Allergy

During a similar time frame, multiple studies evaluated an adult-onset allergy presenting with recurrent urticaria, angioedema and anaphylaxis, with the only identifiable trigger being consumption of red meat 4 to 6 hours before symptoms.[10,11] Platts-Mills and colleagues discovered that these patients had IgE antibodies that were comparable to the antibodies found in patients who reacted to cetuximab. His studies confirmed that the patients who reported delayed allergic reactions to meat also had IgE specific to alpha-gal.[8]

As more research emerged, it became clear that cases of delayed anaphylaxis to red meat were occurring in the same southeastern region as the reactions to cetuximab. This area included Virginia, North Carolina, Tennessee, Arkansas, southern Missouri, and eastern Oklahoma.[12] As the Centers for Disease Control and Prevention classifies this as the endemic area of Rocky Mountain Spotted Fever, researchers were suspicious that this anaphylaxis may be related to prior tick exposure. Indeed, these inquiries confirmed a strong association between a history of tick bites and hypersensitivity symptoms with red meat.[9]

The Tick Bite Theory

Evidence for the association of alpha-gal syndrome and ticks was initially anecdotal with many patients reporting that their meat allergy began following multiple tick bites. This "tick bite theory" helped to explain why the allergy was developing later in life in previously unaffected individuals, and why sensitization was geographically associated with the southeastern United States. Eventually the presence of alpha-gal in the gastrointestinal tract of ticks was confirmed and multiple

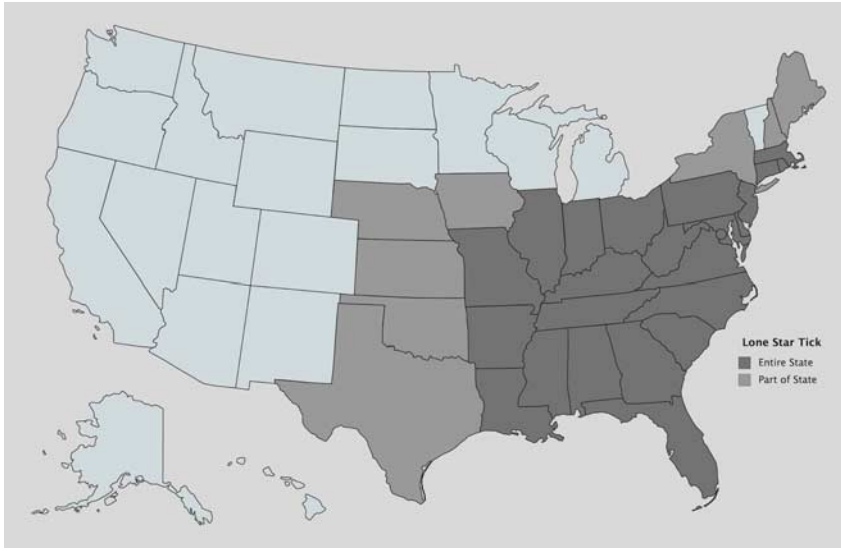

Figure 1. *Illustrative map of the United States demonstrating endemic region for the lone star tick, correlated with alpha gal syndrome. Data gathered from the Centers for Disease Control and Prevention.* full color online

studies were able to demonstrate a correlation between IgE antibodies to tick proteins and IgE antibodies to alpha-gal.[13–15] This pointed to a causal relationship between multiple tick bites and IgE sensitization to alpha-gal in susceptible individuals. A current theory for the mechanism behind alpha-gal sensitization is that the stomach contents of the tick are regurgitated into the skin during the bite. However, the origin of alpha-gal's presence in ticks still needs to be explored.[7]

The first tick species to be implicated in alpha-gal syndrome was *Ambylomma americanum* (lone star tick) in the southeastern United States (Fig. 1). Since then, epidemiologic data has linked other tick species to meat allergy such as in northern Wisconsin and northern Minnesota, where *Dermecentor variabillis* (wood tick) is endemic.[16] Alpha-gal has since been identified in a number of countries—from the United States, to Sweden, to Japan—and as awareness of alpha-gal syndrome increases, so too will its global prevalence.[12,17]

■ Diagnosis

Diagnosing alpha-gal syndrome can be challenging due to the unreliability of conventional allergen tests as well as the variability in clinical presentation. Random cohort studies of subjects in the southeastern United States have identified at least 15% of the population with anti-alpha-gal IgE, but not all patients who are sensitized experience

allergic reactions. Thus, measuring IgE titer levels is necessary but not sufficient alone to make the diagnosis.[18] Currently, alpha-gal syndrome is an integrative diagnosis supported by serum studies, patient history, and clinical presentation.

Clinical History

Alpha-gal syndrome will classically present in an adult who has previously eaten meat without any complications. The reaction itself can vary in severity from localized hives or angioedema to severe anaphylaxis. One case series reported the most common symptoms following meat ingestion were cutaneous pruritus and urticaria followed by gastrointestinal symptoms and anaphylaxis.[19] However, some individuals can experience gastrointestinal symptoms without any cutaneous manifestations which makes the presentation difficult to identify as allergic in nature. The gastrointestinal symptoms of nausea, diarrhea, and indigestion can appear very similar to irritable bowel syndrome, further complicating the diagnosis. Interestingly, patients with this allergy develop symptoms after ingestion but not in response to contact or inhalation exposure.

While most IgE-mediated food allergies are rapid in onset, an unexpected feature of the IgE-mediated reactions caused by alpha-gal is the delayed onset that occurs 3 to 6 hours after ingestion. Given a typical dinner time and the usual delayed response, patients will report onset of symptoms late at night. This delay in symptom presentation is currently theorized to be due to the carbohydrate structure of alpha-gal (since most food allergens are proteins) and can make it difficult to pinpoint the origin of the reaction.[12] The alpha-gal moiety exists in a lipid-bound state and is absorbed in the gastrointestinal tract more slowly and via different mechanisms than proteins. Furthermore, one study revealed that alpha-gal molecules are able to cross intestinal epithelial cells and activate the basophilic allergic response only when bound to lipids.[20] This suggests that glycolipids are the potential allergenic molecules in this syndrome.

A challenge to successful diagnosis of alpha-gal syndrome is that the reactions to meat can be variable and inconsistent between patients and even between exposure-to-exposure for the same patient. Although not every exposure causes a clinical reaction, most exposures will still lead to some reaction and avoidance of red meat has been confirmed to stop the reactions from occurring in these patients (assuming that the patient is not exposed to alternative sources of alpha-gal). This intraindividual variability is believed to potentially reflect differences in the quantity or form of alpha-gal present in different forms of meat, and there has been evidence that lean meat is less likely to trigger reactions compared with fatty cuts.[21,22]

Age should not rule out the syndrome as children have also presented with alpha-gal syndrome features including IgE titers, the delay between

meat ingestion and reaction, the association with tick bites, and the positive resolution of reactions following dietary restriction.[23]

While the classic presentation of alpha-gal syndrome involves delayed symptoms following ingestion of alpha-gal, symptoms can also occur rapidly and severely if the route of administration is more direct. For example, intravenous infusion of alpha-gal-containing cetuximab produced immediate reactions in alpha-gal sensitized patients. Additional research has identified that *in vitro* activation of basophils occurs within 20 minutes of exposure to alpha-gal and intradermal skin tests to cetuximab develop within 15 minutes. This suggests that the delayed onset of symptoms after ingestion is due to the time involved in digesting, absorbing, and transporting the alpha-gal antigen to mast cells in the periphery.

Blood Work

Conventional techniques for detecting food allergy have low sensitivity and specificity in the diagnosis of allergy to meats.[24] Since skin prick tests were found to be inaccurate and resulted in false-negative results, the preferred diagnostic method for alpha-gal is quantification of IgE antibodies.[25] The immunoassay for IgE to alpha-gal (ImmunoCAP specific IgE blood testing) is commercially available, well documented, and recently Food and Drug Administration (FDA) approved.[26]

While alpha-gal IgE is a sensitive marker in allergy care settings, at present there is no accepted cut-offs for IgE quantification. Furthermore, this quantification has limited predictive value for the severity of the allergy.[27] In addition, some recommend concurrent measurement of total IgE because some cases can be nonatopic with low total IgE.[28]

Again, diagnosis of alpha-gal syndrome based on IgE antibodies to alpha-gal has limitations since not all patients with elevated titers (indicating sensitization) will develop anaphylaxis. A basophil activation test has been proposed as an alternative to differentiate symptomatic from asymptomatic patients with elevated titers and has shown promise, but is currently only used in experimental settings and has not been easily implemented.[18] Future research can examine the efficacy of using tick sialome immunoreactive proteins and immune response markers serum or messenger ribonucleic acid level as a complementary method of diagnosing alpha-gal syndrome.

■ Clinical Ramifications

In the southeastern United States and parts of Europe, Asia, and Australia, there is growing awareness of alpha-gal syndrome as the cause of delayed allergic reactions following ingestion of mammalian meat.

Table 1. *Potential Products With Alpha-gal Content*

Medications	Notes
Acetaminophen	May contain magnesium stearate
Naproxen	May contain magnesium stearate
Lisinopril	May contain magnesium stearate
Hydrocodone	May contain magnesium stearate
Clonidine	May contain magnesium stearate
Ibuprofen	May contain glycerin
Heparin	Porcine or bovine-derived
Surgical Products	Notes
Povidone-iodine	May contain glycerin
Bioprosthetic heart valves	Porcine or bovine-derived
Catgut sutures	Mammalian-derived
Other	Notes
Vaccines	May contain gelatin

Even with cessation of meat intake, the potential for anaphylaxis still exists in these patients due to alpha-gal's presence in medical therapeutics. As seen with the reactions to cetuximab, animal-derived medications may inadvertently contain the alpha-gal moiety. In fact, multiple studies in the perioperative setting have demonstrated reactions to animal-based products in alpha-gal syndrome patients such as gelatin-based colloids, heart valves, heparin, and hemostatic agents.[29–31] These reactions range in severity from transient cutaneous symptoms to full blown anaphylaxis and must be considered when caring for patients with alpha-gal syndrome. However, suspicion for the presence of alpha-gal should not be limited to animal-based therapeutics as there are many opportunities for food and other non-mammalian products to have animal products added during preparation or manufacture.[32] Currently the FDA does not require that manufacturers communicate alpha-gal content or their inactive ingredients and thus evidence for the presence of alpha-gal is inconsistent, ranging from obvious (cetuximab) to products that only have a minor mammalian-derived constituent (glycerin or magnesium stearate). While the data are insufficient for drawing firm conclusions, clinicians can still build a framework for determining the relative risk and how to safely manage alpha-gal syndrome.[8] The following are examples of common products that have been investigated for alpha-gal complications (Table 1).

Gelatin

The recent detection of alpha-gal in gelatin has raised suspicion that alpha-gal IgE is the cause of reported allergic reactions to gelatin.[29] This has ramifications not only in foods that contain gelatin—such as marshmallows and candies—but also in vaccines, as gelatin is often added to several vaccines as a stabilizer and reactions have been reported in patients sensitized to alpha-gal.[33]

Magnesium Stearate

Magnesium stearate is a form of stearic acid used in the manufacture of many medications in tablet, capsule, or powder form. Magnesium stearate can be derived from either bovine or plant sources and may be present in the final product of common pain-relieving drugs such as acetaminophen and Percocet (acetaminophen mixed with oxycodone). A study from New Jersey reported a case where a patient with known alpha-gal allergy had multiple allergic reactions to medications that were prepared with magnesium stearate including acetaminophen, naproxen, lisinopril, hydrocodone, and clonidine. Magnesium stearate was the only inactive ingredient in common among the allergies and the patient was able to tolerate the same drugs in forms that did not contain magnesium stearate.[34] Careful evaluation should thus be given to any therapeutics given in the postoperative setting.

Glycerin

Glycerin is a polyol structure used in drug manufacturing to maintain lubrication and hydration, amplifying the effect of the chemical compound's active ingredients. Similar to magnesium stearate, glycerin can be derived from either animal or plant sources and thus may cause reactions in alpha-gal syndrome patients.

Heparin

Heparin is a controversial therapeutic due to recent reports of adverse reactions in alpha-gal allergy patients. Although heparin is derived from either porcine intestine or bovine lung sources, there is little evidence as to whether it intrinsically contains alpha-gal epitopes.[34] Potential remains for alpha-gal to be a "contaminant" but the widespread use of heparin with few reports of anaphylaxis suggests that clinically significant reactions are uncommon.[34] As with any drug reaction, anaphylaxis is dependent on the source, quality of processing, purity of the product, and quantity of the dose. The reported complications following heparin administration to alpha-gal patients have been associated with high-dose heparin given during cardiac bypass procedures, and the risk of a reaction seems to rise with increased dose.[35]

One group of clinicians reported success in pretreating several patients with steroids and antihistamines before heparin initiation. This group also recommended performing a heparin challenge before the procedure, testing the drug response by using the same preparation as they would for the surgery itself.[36]

Enzymes

Patients with alpha-gal syndrome have also been shown to react to recombinant human proteins from nonprimate mammals. One case

series demonstrated that 5 of 9 patients with alpha-gal had specific IgE antibodies for activated recombinant human coagulation factor VII.[37]

It has been shown that alpha-gal is present in mammalian thyroglobulin.[38] However, there have been no reports of alpha-gal allergic reactions due to thyroid hormone supplements. One case report documented a patient with alpha-gal syndrome who was given a plant-based compound levothyroxine preparation instead of the commercially available thyroid formulations which can contain meat byproducts.[39]

Surgical Products

The implications of alpha-gal allergy differ depending on the surgical discipline. For example, in cardiac surgery, bioprosthetic heart valves are of concern due to their derivation from bovine or porcine pericardium. Cases have shown hypersensitivity reactions to the bioprosthetic valves or premature deterioration of these valves in alpha-gal syndrome patients.[31,40] Current literature recommends the use of decellularized valves without alpha-gal for these patients.

■ Role of the Clinician

In geographic areas where sensitization is present, clinicians must be aware of potential interactions and ask patients about any history of meat allergies during preoperative planning. While a positive history would not necessarily prevent the use of animal-derived products, clinicians need to be prepared to detect any potential reactions quickly. Some cases have reported reasonable success in premedicating alpha-gal allergy patients with steroids and diphenhydramine to prevent potential cross reactivity.[4]

The first step for safe care of these patients is proper identification. Because of the recent discovery of this syndrome and its unusual nature, patients will likely present with a variety of diagnoses or clues that need to be recognized as representative of alpha-gal syndrome. Furthermore, patients may also present for surgery with labels such as meat allergy, red meat allergy, or quadruped allergy that need to be explored for potential alpha-gal syndrome.[41] Patients who have undergone prior cancer treatment may report an allergy to cetuximab, specifically anaphylaxis upon first administration. These clues should prompt the clinician to perform further questioning and to maintain a high suspicion for alpha-gal syndrome, particularly if the clinician is practicing in the southeastern United States or if the patient previously lived in that region. Risk factors such as A and O blood type and tick bite history may aid in identification but are not considered essential for clinical diagnosis.[42] Once identified, this syndrome should be properly documented in the medical record and precautions should be taken.

Platts-Mills and colleagues recently attempted to categorize food and medical products that may produce a reaction in alpha-gal syndrome, stratified by relative risk. Medical products with the highest risk that should be avoided included cetuximab and the gelatin-based colloid plasma substitute (Gelafundin).[29,30] Therapeutics that are known to contain alpha-gal and should be used with caution included gelatin-containing vaccines [shingles, measles-mumps-rubella (MMR), yellow fever],[33] bovine and porcine heart valves,[38] and anti-venom. Finally, there are products with insufficient data and limited evidence suggesting that they may contain alpha-gal and cause reactions in some alpha-gal syndrome patients. These include medications that contain gelatin such as capsules, surgifoam powders, gabapentin oral solution, and lidocaine patches.[34]

Some clinics in the southeastern United States have had their pharmacists compile alpha-gal information about as many drugs as possible to help guide perioperative counseling. As drug formulations are mutable and can very among manufacturers, an accurate list will vary from institution to institution based on the mix of suppliers and inactive ingredients (Table 2). This makes consistent identification challenging.

Similar to the allergic reactions to meat, anaphylaxis to alpha-gal-containing medications can vary in severity and timing due to differences in the alpha-gal content of each medication and the route of administration. As seen with cetuximab, intravenous administration will result in quicker onset of symptoms while oral administration (as seen with red meat) can result in delayed presentation. Cofactors such as the specific patient's IgE titer may also play a role; thus, risk-benefit analysis for the use of each drug should be performed for each patient individually.[43,44]

Complications can also arise from inactive compounds found in the specific drug preparation/iteration rather than in the active drug itself. In cases where the original source of a substance such as lactic acid or stearic

Table 2. *Inactive Ingredients With Alpha-gal*

Inactive Ingredients That May Be Animal Derived	Examples of Therapeutics That Contain Inactive Ingredient
Gelatin	Vaccines, celecoxib, pregabalin, gabapentin capsules
Magnesium stearate	Acetaminophen, Oxycodone, naproxen, lisinopril, clonidine
Glycerin	Commercial povidone-iodine, ibuprofen, methadone solution
Hyaluronidase	Vitrase,* Amphadase†
Lactic Acid	Polygalactin (Vicryl) sutures‡

*Manufacturer: Siegfried Irvine.
†Manufacturer: Amphastar Pharmaceuticals.
‡Manufacturer: Ethicon Inc.

acid cannot be determined, some studies have deemed medications containing these substances as unsafe for alpha-gal syndrome patients.[45] Unfortunately, many manufacturers do not report or know the full etiology of each substance used, and they do not currently report alpha-gal content in their final product. Inactive ingredients can change at any time and currently the FDA does not require manufacturers to communicate this information[34]; therefore, attention must be also given to the inactive ingredients in each drug given to an alpha-gal syndrome patient.

■ Importance for Ophthalmologists

The impact of increasingly prevalent alpha-gal allergies on ophthalmic surgery is currently unknown. There is no current data on whether topical or intraocular exposure to alpha-gal can trigger anaphylaxis in a susceptible patient. Still, although much of the literature on treating alpha-gal allergy is limited to case reports, these studies reveal strong associations which can help clinicians carefully evaluate and mindfully treat these patients.[46] The pharmacology literature has taken the stance that affected patients should avoid any medication that may contain the alpha-gal epitope.[47] They have pointed out that alpha-gal can be found in products such as Creon 10[48] and xenografts. The anesthesiology literature states that while anecdotal experience indicates that hypersensitivity reactions may recede with time in the absence of recurrent exposures, there is no guarantee a patient will not react poorly to substances in the perioperative period.[42] Thus, we would recommend being vigilant and avoiding alpha-gal products whenever possible. If necessary, treatment for patients experiencing alpha-gal allergy should be similar to the treatment for any hypersensitivity reaction, including antihistamines, corticosteroids, albuterol, and epinephrine.

Systemically, health care systems in the southeastern United States should prioritize education for all relevant providers on this novel syndrome. Ophthalmologists should work in unison with their pharmacists and anesthesiologists to initiate an orderly process of identifying these patients and maintaining an up to date list of medications with alpha-gal content. A sample list of known medications that have been verified with drug manufacturers for presence of alpha-gal, magnesium stearate, stearic acid, lactic acid, glycerin, and gelatin is shown below (Table 3).

■ Ophthalmic Surgery Implications

Sterile Preparation

Glycerin is noteworthy in the surgical field for its role as an inactive ingredient of povidone-iodine (Betadine, Alcon), an essential component

Table 3. *Partial Alphabetical List of Medications and Surgical Adjuncts Theoretically Safe for Use for Patients With Alpha-Gal Syndrome*

Anesthesia Drugs	Manufacturer
Atropine	Hospira (1 mg/10 mL) and American Reagent (0.4 mg/1 mL)
Chondroitin sulfate	Alcon (Viscoat)
Dexamethasone	Fresnius Kabi
Diphenhydramine	App IV
Epinephrine	Hospira (1 mg/10 mL) and BPI (1 mg/1 mL)
Hydrocortisone	Pfizer
Hydromorphone	Fresnius Kabi (1 mg/1 mL)
Midazolam	Hospira (2 mg/2 mL) and Westward (10 mg/2 mL)
Morphine	Fresnius Kabi (2 mg/mL) and Westward (4 mg/mL)
Ondansetron	Westward
Phenylephrine	Avadel
Promethazine	Westward
Propofol	Fresnius Kabi
Rocuronium	Fresnius Kabi
Sodium hyaluronate	Alcon (Provisc) and Abbot (Healon)
Succinylcholine	Hospira

Disclaimer: Information taken from manufacturer package inserts. Information subject to change based on medication manufacture. Please contact pharmacy and review medications before ordering.

of antiseptic surgical preparation. With the capacity to be either plant or animal-derived, a formulation with glycerin could trigger an alpha-gal allergy. To prevent potential complications, surgical centers in the southeastern United States should be prepared to identify and use verified Betadine® mixtures in alpha-gal syndrome patients.

Hyaluronidase

Hyaluronidase is an enzyme used as an additive to local ocular anesthetic blocks to accelerate the onset of anesthesia and reduce ocular movements during surgery. Traditionally a mammalian-derived compound, there is potential for alpha-gal contamination and thus should be used with caution in alpha-gal syndrome patients. Examples of unsafe ophthalmic hyaluronidase blocks include ovine-derived Vitrase (Siegfried Irvine), bovine-derived Amphadase (Amphastar Pharmaceuticals), and Hylenex (Halozyme), a human recombinant that is derived from Chinese hamster ovary cells.[49]

Topical Glycerin, Collagen Shields, and Contact Lenses

There are no reports of topical corneal exposure to glycerin or glycerin-containing compounds inducing an alpha-gal anaphylactic reaction. Similarly, there is no evidence for or against the use of corneal collagen shields or contact lenses in this patient population. Given the

ubiquity of contact lenses, one would expect that if there was an association with alpha-gal allergy that it would have been already reported; that being said, we would recommend making a medical judgment of the necessity of any of the above by weighing benefits of therapy versus theoretical risks.

Ophthalmic Viscosurgical Devices (OVD)

These agents are used to create and maintain space in the anterior chamber of the eye and protect the corneal endothelium during cataract surgeries and implantation of an intraocular lens. Many of these agents contain hyaluronidase in their solution and must be vetted for the origin of the hyaluronidase. Vegan OVDs like sodium hyaluronate (Provisc, Alcon) that are obtained through bacterial fermentation can be considered safe for alpha-gal syndrome patients. However, animal-derived OVDs may also be safe depending on the source. As mentioned previously, alpha-gal is found in *nonprimate mammals* so using OVDs produced from nonmammalian sources should theoretically be safe to use in alpha-gal syndrome patients. Examples of these OVDs include chondroitin sulfate (Viscoat, Alcon) which is derived from shark fin cartilage, and sodium hyaluronate (Healon, Abbot) which is avian-derived.

Suture Materials

Certain suture materials should also be avoided. Catgut sutures, which are manufactured from the small intestines of alpha-gal-containing mammals, have been linked to reports of allergic reactions and wound breakdown.[50] Synthetic sutures such as polyglactin 910 (Vicryl, Ethicon Inc.) could also theoretically induce an allergic response due to its animal-derived lactic acid coat; however, this requires further investigation.[42] Although studies are still inconclusive for surgical products such as biologic mesh and other topical hemostatic agents, safety of these therapeutics should be carefully discussed before use.

■ Conclusion

Open communication between the surgical team, anesthesia team, and nursing staff regarding potential complications and signs of alpha-gal syndrome can help identify and prevent allergic reactions from occurring. Prolonged postoperative observation should be standard in these patients, and thus we recommend scheduling these patients as the first operation of the day.

As a relatively unknown allergy, alpha-gal syndrome has the potential to be the unintentional source of negative outcomes in both medical and surgical settings. It is the role of ophthalmologists to be cognizant of this allergy and be mindful of the medical and surgical products that they use

in these patients. While some products do not have alternatives, other therapeutics can and should be switched out for safer alternatives.

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