



Meat Allergy: A Ticking Time Bomb

Rohan Shah¹ · Robert A. Schwartz¹

Accepted: 21 April 2022 / Published online: 16 May 2022
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

Abstract

Food allergies are relatively prevalent, but mammalian meat allergy remains uncommon and represents an important, potentially acute healthcare risk. This risk is partly because both clinicians and the public lack awareness of this serious allergy, which is unique in three important ways: it incurs a delayed reaction, it is induced by a carbohydrate rather than a protein, and it is linked to tick bites. Although various symptoms are possible, its unique presentation means that mammalian meat allergy is often presented to the dermatologist. We review this challenging subject, which is particularly salient considering the unique connection between ticks and mammalian meat allergy, the expanding tick territory, and the dependency by so many on meat products, not only in the diet but also in medications and medical devices.

Key Points

Mammalian meat allergy challenges conventional thoughts about food allergy with its delayed symptom onset driven by immunoglobulin E antibodies to a carbohydrate rather than a protein and its unique connection with ticks.

The cutaneous presentations of mammalian meat allergy mean the dermatologist may play an integral part in identifying this allergy and in advocating for better history taking and vigilance in choosing medical treatments.

The severe symptoms, perioperative contraindications, and expanding research on this allergic condition requires a multidisciplinary effort, especially since the prevalence of alpha-gal syndrome is projected to increase with the rise in tick bites and the migratory patterns of ticks.

1 Introduction

Mammalian meat allergy, like most food allergies, may lead to anaphylaxis. Although meat allergy is uncommon, reported cases continue to rise, affecting children and adults worldwide (Fig. 1). It develops in those previously tolerant of mammalian meat [1]. In the USA alone, the number of confirmed cases of mammalian meat allergy has risen from only 12 in 2009 to 34,000 in 2019. Until recently, mammalian meat allergy was considered rare and was described primarily in young atopic children without an established pathologic mechanism [2]. The galactose-alpha-1,3-galactose (alpha-gal) is one of very few carbohydrate allergens known to induce anaphylaxis and, rarely, death [3]. Perhaps most interesting is the unique role that tick bites have in sensitization to mammalian meat, manifesting as “alpha-gal syndrome” [1]. A history of tick bites may predispose a patient to meat allergy and subsequent life-threatening symptoms that can resolve within a year but may also persist for many years. Usually, the patient may resume eating mammalian meat within 3–4 years provided there are no further tick bites, as alpha-gal immunoglobulin E (IgE) reduces significantly within 18–24 months [2].

2 History

Multiple discoveries were integral in elucidating the unusual connection between tick bites and meat allergy. Between 2003 and 2007, 25 patients in Sydney, Australia,

✉ Rohan Shah
rs1520@njms.rutgers.edu

¹ Department of Dermatology, Rutgers New Jersey Medical School, Newark, NJ, USA



Fig. 1 Announcement posted at the Intercontinental Hotel, Kunming, China, advising the public that meat allergy may be less common than other food allergies but is still important

presented with a history of allergic reactions to red meat notable for urticaria, angioedema, respiratory distress, and syncope. All patients lived in areas infested with several endemic tick species, and all patients gave a history of large local reactions to tick bites. These findings suggested a novel association between tick bite reactions and mammalian meat allergy [4, 5]. In a 2008 clinical trial of the monoclonal antibody cetuximab, patients with cancer developed severe delayed-type allergy due to the presence of IgE antibodies to alpha-gal before their first exposure to the treatment. In the same year, an increasing number of patients with delayed-type mammalian meat allergy was reported across the USA, especially in the southeast. This association between tick and alpha-gal hypersensitivity became more evident when IgE prevalence overlapped the geographical distribution of *Amblyomma americanum*. When patients without previous exposure to cetuximab experienced severe anaphylaxis on initial exposure, alpha-gal syndrome was coined to describe a delayed allergic reaction to alpha-gal following consumption of mammalian meat [6].

3 Epidemiology

Ticks (Ixodidae) are bloodsucking parasites and have long been recognized as a source of infection because they spread many viral, bacterial, and rickettsial diseases. Tick saliva contains a spectrum of proteins responsible for anti-hemostatic and immunomodulatory functions that aid the tick in successfully attaching to and feeding from the host. The host organism generates an immune response to tick saliva to mitigate future tick attachment [7].

Tick-borne illness is no oddity. Lyme disease is a commonly recognized multisystem zoonosis with worldwide prevalence, specifically in tick-endemic regions, including North America, Europe, and parts of Asia. *Ixodes* ticks carrying pathogenic strains of *Borrelia burgdorferi* transmit infection while feeding on vertebrate hosts. Anti-inflammatory proteins produced by both *Borrelia* and its tick vector provide resistance against the initial host defense. The classical skin finding in Lyme disease is erythema migrans, which stems from skin infection to *Borrelia* rather than an allergic reaction [8]. Patients infected with ticks carrying Lyme disease develop specific IgM and IgG antibodies critical for serological testing. On the other hand, ticks such as *A. americanum* and *Ixodes ricinus*, which contain alpha-gal in their saliva, induce alpha-gal-specific IgE antibodies that render the host potentially sensitized to mammalian meat [9].

Although there is no current estimate of the global prevalence of alpha-gal syndrome, self-reported and physician-diagnosed cases have been described in most regions of the world, with the highest volumes in Australia, the USA, Germany, Sweden, Canada, and South Africa [9]. Of these, Australia has the highest prevalence, with 113 cases/100,000 people, followed by Virginia, USA, with 13 cases/100,000, and Baden-Württemberg, Germany, with four cases/100,000 [10]. Mammalian meat allergy is common in a large portion of the USA and is most prevalent in the southeast, deep south, and midwest and along the Atlantic coast [6]. Epidemiologic studies of case numbers provided by physicians, along with serological studies in regions known to have a high occurrence of mammalian meat allergy (including areas of Alabama, Arkansas, Kentucky, Missouri, North Carolina, Oklahoma, and Virginia), found that regions in which the lone star tick, or *A. americanum*, was endemic had the highest prevalence of alpha-gal syndrome. The prevalence of alpha-gal syndrome cases conformed well to the geographical distribution of *A. americanum*. In the northeast USA, other tick species may be responsible for promoting allergy, including the endemic *Dermacentor variabilis* and *Ixodes scapularis*. Both have been shown to cause alpha-gal sensitization in regions outside of the USA, including Japan, Europe, and Australia [11].

Curiously, not all regions in which the lone star tick was endemic had a high prevalence of mammalian meat allergy. The fire ant (*Solenopsis* spp.) is an ecologic competitor to the tick and is endemic in certain states, including Texas. An epidemiologic study by Wilson et al. [11] indicated a negative correlation between alpha-gal cases and established fire ant colonies. This suggests that expansion of the fire ant into parts of the American southeast and midwest may control the population of lone star ticks and thereby decrease cases of tick-related meat allergy [11]. This may have important implications as the lone star tick population gradually migrates into northern regions of the USA. It also warrants improved understanding of tick-induced meat allergy among all physicians, regardless of geographical location.

Alpha-gal syndrome is a global entity, but certain regions have notably higher rates of mammalian meat allergy. Naturally, these are also areas in which various tick species are endemic. In Japan, the *Haemaphysalis longicornis*, a vector for Japanese spotted fever, was a primary vector for alpha-gal sensitization in the Shimane prefecture, a Japanese region notable for high cases of mammalian meat allergy. A study from this region of 30 patients with mammalian meat allergy found that 24 patients had serum IgE reacting with water-soluble salivary gland protein of *H. longicornis*, a reaction mediated by alpha-gal binding [12]. The tick, specifically *I. Ricinus*, is also endemic to Sweden. In the past 6 years, more than 200 cases of mammalian meat allergy have been diagnosed. In a Swedish report of 39 adult patients with the allergy, all had IgE antibodies to alpha-gal and displayed urticaria hours after consuming red meat [13]. Exposure to *I. ricinus* has increased over the last decade in Sweden, and ticks are extending north and westward from the country, suggesting the possibility of future increases in meat allergy in other European nations [14].

Ixodes holocyclus is responsible for nearly 95% of tick bites in Eastern Australia and for an increased incidence of mammalian meat allergy in Australia (Table 1). A nationwide study of adult-onset mammalian meat allergy and reactivity to gelatin was consistent with similar studies that found historical associations with tick bite. Beef was the mammalian meat most commonly known to cause symptoms, mainly because of its increased consumption in the region [15].

4 Clinical Findings, Symptoms, and Recognition

Mammalian meat allergy deviates from the current understanding of food allergy because exposure to an ectoparasite is critical for IgE antibody-mediated pathophysiology and clinical symptoms are delayed rather than immediate. Clinical findings associated with alpha-gal syndrome vary from urticaria to anaphylactic shock. Although mammalian meat allergy is mostly described in adult patients, the condition has also been reported in children. Both populations present similarly with delayed urticaria, angioedema, generalized pruritus, anaphylaxis, and gastrointestinal symptoms [16]. The severity of mammalian meat allergy is represented by its tendency to induce anaphylaxis in up to 60% of patients [1]. The most common allergic manifestations include urticaria and angioedema, seen in up to 99% of patients [9, 17]. Some variation does exist in the adult population according to whether the cutaneous or gastrointestinal manifestations are most severe. Exfoliative erythroderma has also been described in patients with mammalian meat allergy, and one case involved > 90% of the body surface area [15]. Since cutaneous findings are the primary symptoms of mammalian meat allergy, the expertise in physical diagnosis offered by dermatologists and their awareness of skin findings common in allergic reactions will be helpful in addressing this allergy.

The IgE-mediated pathophysiology of food allergies means they have an immediate-onset reaction, often within seconds to minutes. An unusual feature of alpha-gal syndrome is that oral ingestion of red meat does not result in immediate symptoms. Rather, typical symptom onset is between 2 and 6 h after ingestion [1]. In a case series of 12 patients with reactions to red meat and positive alpha-gal IgE titers, the earliest symptom onset was 150 min [18]. A separate study conducted in alpha-gal-sensitized subjects who consumed pork kidney demonstrated symptom onset between 120 and 750 min following ingestion [19]. Furthermore, repeated ingestion of the offending agent has not been shown to expedite symptom onset [9, 20].

The delay in symptom presentation in mammalian meat allergy may suggest the involvement of variables other

Table 1 Common ticks implicated in mammalian meat allergy and their geographical distribution

Tick	Endemic region	Migratory location
<i>Amblyomma americanum</i>	Southeast, midwest, and mid-Atlantic USA	Northern/northeast USA
<i>Ixodes ricinus</i>	Eastern Europe, Scandinavia, North Africa, and Middle East	Northern and Western Europe
<i>Ixodes holocyclus</i>	Eastern Australia	New Zealand
<i>Haemaphysalis longicornis</i>	Shimane prefecture in Japan	New Zealand, Korea, China, and Fiji

than an IgE-mediated reaction in the pathophysiology of alpha-gal syndrome [15]. Unlike most food allergies, mammalian meat allergy develops IgE antibodies to a glycan rather than a protein, likely causing abnormal digestion, absorption, and transit of the relevant glycoproteins. This abnormal release and absorption of the alpha-gal moiety is likely the reason for the delayed reaction [15, 21].

Although the mechanism of alpha-gal syndrome remains unclear, an understanding of the variable clinical findings can provide further insight into the unique allergic response. This variability has been shown to depend on environmental factors, including exercise and alcohol intake, which alter the severity and speed of symptom onset in both conventional allergic response and alpha-gal syndrome [22]. The amount of alpha-gal consumed from mammalian meat also influences the severity and speed of the allergic response. Individuals who consume organ meats with higher amounts of alpha-gal may present with higher concentrations of the glycan, higher concentrations of IgE antibodies, and faster onset of symptoms [23]. Conversely, consumption of mammalian meats high in fats, such as steak, may delay symptom onset [22]. However, since motilin release is stimulated by fats, such fatty meats may move more quickly through the small intestine, contributing to a reduced opportunity to generate an allergic reaction. Other plausible factors mediating mammalian meat allergy include the number of tick bites the patient has experienced, the timing of these tick bites, and whether a local reaction to the tick bite occurred. A doubling of alpha-gal IgE levels was noted in subsequent bites from the Australian tick, *Ixodes australiensis* [24].

5 Implications

Treatment of meat allergy, like that of other food allergens, involves avoiding the offending agent. For most in the USA, this means avoiding beef, pork, and lamb. Internal organs such as the kidneys, liver, heart, and intestines should also be avoided as they can induce reactions. Mammalian animals

that are commonly consumed in the USA and other countries and should be avoided include rabbit, horse, goat, deer, kangaroo, and bear (Table 2). It is important for the patient to understand that an allergic reaction to one of these meats is an indicator that all mammalian meats should be avoided [25]. Patients must be aware of hidden sources of alpha-gal, including beef broth, animal fat, and dairy products [25]. This usually requires substantial alterations to the diets of many who rely on mammalian meat as a significant protein source, and a nutritionist’s expertise and help may be required to develop a new diet [9].

Aside from avoiding the traditional sources of mammalian meat, the patient with alpha-gal syndrome must consider other factors that can exacerbate symptoms. Intravenous medications with high alpha-gal content, including cetuximab and gelatin-based colloid agents, may also need to be avoided after weighing the risks and benefits. For patients with a high risk of mammalian meat consumption following alpha-gal syndrome diagnosis, an intramuscular epinephrine injection may be required to arrest future reactions and prevent the possibility of an anaphylactic reaction [26]. Corticosteroids and antihistamines may also be required if the reaction is more severe [9]. The requirement for epinephrine auto-injectors can have profound medical, social, and financial implications for patients with a tendency to develop anaphylaxis following mammalian meat ingestion [27]. For instance, individuals who may not otherwise carry a backpack or purse may need to do so to ensure an epinephrine auto-injection is available at all times.

The connection between ticks and mammalian meat allergy warrants an emphasis on secondary prevention by avoiding ticks and practicing adequate tick-removal techniques, especially in endemic areas [28]. This is becoming more difficult as ticks are spreading to and becoming endemic in more regions [11]. Upon tick bite exposure, a careful assessment of the risk of anaphylaxis, including serological analysis for alpha-gal IgE, should be conducted [29]. The patient should refrain from consuming mammalian meat

Table 2 Lifestyle changes required to avoid alpha-gal allergic reactions following meat sensitization and implications of these changes

Lifestyle changes	Implications
Avoidance of beef, pork, lamb, rabbit, horse, goat, deer, kangaroo, and bear meat	Requires novel sources of protein in diet. Emphasis of nonmammalian meat in diet (i.e., chicken, seafood)
Caution for beef broth, animal fat, and dairy products	
Avoidance of ticks; adequate tick-removal techniques	Avoidance of tick-endemic regions. Education on proper tick-removal techniques
Physician and patient efforts to avoid medications known to contain alpha-gal and induce allergic reactions	Physicians confined to the use of certain medications. Common conditions such as hypothyroidism and hypertension may require other therapeutic agents. Patients should check all medications for alpha-gal
Possible use of intramuscular epinephrine injections	Social and financial adjustments for the patient

to decrease chances of an adverse reaction until they receive the serologic results [25].

Given the unique symptom-onset profile of mammalian meat allergy, special considerations must be noted by the patient and provider. For instance, mammalian meat is frequently consumed during dinner. The onset of symptoms usually starts 2–3 h and sometimes even 4–6 h after meat ingestion [30]. As a result, patients are likely to present to the emergency department with reactions that occur late at night, often awakening them from sleep [30]. Therefore, emergency medicine providers are another vital part of the care team that should be aware of this allergy in order to adequately identify and treat alpha-gal syndrome.

It has long been suspected that allergens can alter immunological responses associated with plaque buildup. Multiple studies have suggested a connection between alpha-gal sensitization and coronary artery disease. A study in 118 patients, of which 26% had alpha-gal antibodies, found that—after adjusting for confounders such as diabetes, hypertension, and medications—those with alpha-gal antibodies also had 30% more plaque buildup in coronary arteries than those not sensitized to the allergen [31, 32]. This association was stronger in those aged < 65 years. A separate study in 1056 patients with suspected coronary artery disease concluded that alpha-gal sensitization was independently associated with noncalcified plaque buildup and occurred at a greater frequency in patients with ST-segment elevated myocardial infarction than in those with no coronary artery disease. Although the exact mechanism remains unclear, one possibility is that an interaction between alpha-gal and IgE activates mast cells and other inflammatory mediators to the coronary artery vessel walls. As confirmed by Vernon et al. [33], it may be beneficial for providers to advise against consumption of mammalian meat if the patient is alpha-gal positive and has established cardiovascular risk factors.

Reports of allergic reactions to drugs and medical devices containing the alpha-gal epitope are also increasing. Many of these reactions stem from inactive substances, such as gelatin or stearic acid, which are often part of the manufacturing process for certain drugs [34]. This is particularly troublesome for clinicians, who will need to be more vigilant in prescribing medications to patients with sensitized alpha-gal antibodies or who have had previous reactions to alpha-gal. Magnesium stearate, derived from bovine sources, contains the alpha-gal epitope and is implicated in numerous drugs, including but not limited to acetaminophen, lisinopril, naproxen, ibuprofen, hydrocodone, haloperidol, pregabalin, hydromorphone, and clonidine (Table 3) [30].

Alpha-gal allergy is also known to complicate treatment options for postprocedural hypothyroidism. Thyroid hormone formulations that involve magnesium stearate include synthetic thyroxine, levothyroxine, synthetic triiodothyronine, and liothyronine [35]. This allergy can also

Table 3 Frequently used medications containing alpha-gal with potential contraindications for patients with alpha-gal syndrome sensitized by ticks

Medications and products	Alpha-gal-containing ingredient
Medication	
Acetaminophen	Magnesium stearate
Alvimopan	Gelatin, bovine and porcine
Aminocaproic acid	Magnesium stearate and stearic acid
Baclofen	Magnesium stearate
Carbidopa-levodopa	Magnesium stearate
Celecoxib	Gelatin, bovine and porcine
Clonidine	Magnesium stearate
Gabapentin	Gelatin, bovine and porcine
Haloperidol	Lactic acid
Heparin	Porcine
Hydrocodone	Magnesium stearate
Hydromorphone	Lactic acid
Ibuprofen	Glycerin
Levothyroxine	Magnesium stearate
Lidocaine patch	Gelatin
Liothyronine	Magnesium stearate
Lisinopril	Magnesium stearate
Metoclopramide	Magnesium stearate
Naproxen	Magnesium stearate
Oxycodone	Stearic acid
Oxycontin	Magnesium stearate
Synthetic triiodothyronine	Magnesium stearate
Synthetic thyroxine	Magnesium stearate
Devices and products	
Bioprosthetic valves	Porcine or bovine derived
Catgut sutures	Mammalian derived

compromise proper ophthalmic care. Hyaluronidase, an additive to local ocular anesthetic blocks to accelerate anesthesia onset and reduce ocular movements during surgery, contains alpha-gal. Finally, suture materials such as catgut sutures manufactured from the small intestines of alpha-gal-containing mammals have been reported to induce allergic reactions [36].

Because heparin is derived from porcine sources, it has been identified as a possible alpha-gal allergy trigger. The widespread use of heparin with minimal reports of allergic reactions suggests that clinically significant reactions are uncommon. The reported reactions to heparin have mostly been related to high-dose heparin in cardiac bypass cases, implying that dose, processing technique, and purity are factors in an alpha-gal-induced reaction [37]. Bioprosthetic heart valves are also constructed with bovine pericardium and are of significant concern. Three cases of patients with mammalian meat allergy who underwent valve replacement with bioprosthetic valves and experienced perioperative

hypersensitivity reactions have been reported. In these patients, the use of decellularized valves should be considered to prevent adverse events perioperatively and premature deterioration of these valves [37].

Further complicating the management of patients with mammalian meat allergy is the use of stearic acid or gelatin as inactive compounds. If derived from animal sources, these compounds may contain alpha-gal and can invoke an allergic reaction in the sensitized patient following administration [30]. However, most manufacturers do not report the lineage of such inactive substances and do not test for alpha-gal content in their drugs. Furthermore, the US FDA does not require dissemination of this information [38]. Thus, the clinician must be especially astute in identifying possible reactions since the same drug from different manufacturers might invoke very different responses.

Allergists, dermatologists, primary care physicians, and emergency physicians have a crucial role in the management of patients with alpha-gal syndrome. First, awareness of this unique syndrome and its manifestation as mammalian meat allergy will enable better history taking and, subsequently, proper diagnostic evaluations. For instance, initial skin prick tests for mammalian meat allergy usually produce only minimal wheals [2]. However, after a complete history, including tick bite status, further testing may show positive intradermal skin tests and reveal IgE antibodies directed to alpha-gal [2]. Ideally, the provider should ask about previous tick bites and note any previous allergic reactions to animal products, especially in tick-endemic regions.

Because these physicians are most equipped to make the diagnosis of alpha-gal syndrome, they also have the responsibility of conveying the extra vigilance needed in prescribing certain medications, most of which are drugs commonly taken for hypertension, perioperative stability, and inflammation. Identification of patients who may be sensitized to alpha-gal will facilitate perioperative management for anesthesiologists and surgeons alike [30]. As awareness increases, patients may present for surgery with identified alpha-gal allergy, but it may be documented as a meat allergy, which could at first appear as an irrelevant food allergy. Patients with cancer may report an allergy to cetuximab, which should also be documented as a clue to prompt further questioning of tick bite history [38]. Standard of care in tick-endemic regions is now to check for alpha-gal IgE before administering cetuximab [39].

6 Conclusion

Unlike Lyme disease, alpha-gal syndrome is a much less known entity, warranting greater awareness of a rare but potentially life-threatening food allergy. It is important that the public be educated about this potential hazard in

restaurants, bakeries, and other venues (Fig. 1). Mammalian meat is a staple in most diets of the world. With the increasing numbers of tick bites, coupled with the gradual migration of ticks, the prevalence of alpha-gal syndrome is projected to increase [40]. Because mammalian meat allergy primarily presents cutaneous findings, the dermatologist is poised to play an integral part in identifying this allergy and advocating for better history taking and vigilance in choosing medical treatments. The severe symptoms, perioperative contraindications, and expanding research on this allergic condition requires a multidisciplinary effort. With its delayed symptom onset, driven by IgE antibodies to a carbohydrate rather than a protein, along with its unique connection to ticks, mammalian meat allergy challenges the conventions of food allergy. Further investigation into symptom variability and the specific mechanism by which ticks induce mammalian meat allergy will prove critical for future diagnostic and therapeutic interventions for this condition.

Declarations

Funding No sources of funding were used to conduct this study or prepare this manuscript.

Conflicts of interest Rohan Shah and Robert A. Schwartz have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent to publish Not applicable.

Availability of data Not applicable—no data.

Code availability Not applicable.

Author contributions RS was primary writer and editor of paper. RS helped foster ideas, edited, and provided significant research sources to help write the manuscript.

References

1. Van Nunen SA. Tick-induced allergies: mammalian meat allergy and tick anaphylaxis. *Med J Aust.* 2018;208(7):316–21.
2. 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.
3. Commins SP. Carbohydrates as allergens. *Curr Allergy Asthma Rep.* 2014;15(1):492.
4. Van Nunen SA, O'Connor KS, Clarke LR, Boyle RX, Fernando SL. An association between tick bite reactions and red meat allergy in humans. *Med J Aust.* 2009;190(9):510–1.
5. Van Nunen SA, O'Connor KS, Fernando SL, Clarke LR, Boyle. The association between Ixodes Holocyclus tick bite reactions and red meat allergy. *RJIMJ.* 2007;37:510–511.

6. Sharma SR, Karim S. Tick saliva and the alpha-gal syndrome: finding a needle in a haystack. *Front Cell Infect Microbiol*. 2021;11:264.
7. Commins SP, Platts-Mills TA. Tick bites and red meat allergy. *Curr Opin Allergy Clin Immunol*. 2013;13(4):354–9.
8. Bhate C, Schwartz RA. Lyme disease: part I. Advances and perspectives. *J Am Acad Dermatol*. 2011;64(4):619–36 (quiz 37–8).
9. Patel C, Iweala OI. ‘Doc, will I ever eat steak again?’ Diagnosis and management of alpha-gal syndrome. *Curr Opin Pediatr*. 2020;32(6):816–24.
10. Fischer J, Yazdi AS, Biedermann T. Clinical spectrum of α -Gal syndrome: from immediate-type to delayed immediate-type reactions to mammalian innards and meat. *Allergo J Int*. 2016;25:55–62.
11. Wilson JM, Keshavarz B, Retterer M, Workman LJ, Schuyler AJ, McGowan EC, et al. A dynamic relationship between two regional causes of IgE-mediated anaphylaxis: α -Gal syndrome and imported fire ant. *J Allergy Clin Immunol*. 2021;147(2):643–652. e7.
12. Chinuki Y, Ishiwata K, Yamaji K, Takahashi H, Morita E. Haemaphysalis longicornis tick bites are a possible cause of red meat allergy in Japan. *Allergy*. 2016;71(3):421–5.
13. Hamsten C, Tran TAT, Starkhammar M, Brauner A, Commins SP, Platts-Mills TAE, et al. Red meat allergy in Sweden: association with tick sensitization and B-negative blood groups. *J Allergy Clin Immunol*. 2013;132(6):1431–4.
14. Apostolovic D, Tran TAT, Starkhammar M, Sánchez-Vidaurre S, Hamsten C, Van Hage M. The red meat allergy syndrome in Sweden. *Allergo J Int*. 2016;25(2):49–54.
15. Schimmel J, Fawaz B, Renzi M, Heymann WR, Van Nunen S, Manders S. Mammalian meat allergy—beyond urticaria? *Int J Dermatol*. 2020;59(8):e312–4.
16. Donaldson B, Le MN. The clinical presentation of alpha-gal allergy among pediatric patients with food allergy in southwest Missouri. *Ann Allergy Asthma Immunol*. 2019;123(5):524–5.
17. Wen S, Unuma K, Chinuki Y, Hikino H, Uemura K. Fatal anaphylaxis due to alpha-gal syndrome after initial cetuximab administration: the first forensic case report. *Leg Med (Tokyo)*. 2021;51:101–18.
18. Commins SP, James HR, Stevens W, Pochan SL, Land MH, King C, et al. Delayed clinical and ex vivo response to mammalian meat in patients with IgE to galactose-alpha-1,3-galactose. *J Allergy Clin Immunol*. 2014;134(1):108–15.
19. Wilson JM, Platts-Mills TAE. Red meat allergy in children and adults. *Curr Opin Allergy Clin Immunol*. 2019;19(3):229–35.
20. Fischer J, Hebsaker J, Caponetto P, Platts-Mills TA, Biedermann T. Galactose-alpha-1,3-galactose sensitization is a prerequisite for pork-kidney allergy and cofactor-related mammalian meat anaphylaxis. *J Allergy Clin Immunol*. 2014;134(3):755–9. e1.
21. Cabezas-Cruz A, Hodžić A, Román-Carrasco P, Mateos-Hernández L, Duscher GG, Sinha DK, et al. Environmental and molecular drivers of the α -gal syndrome. *Front Immunol*. 2019;10:1210.
22. Rutkowski K, Wagner A, Rutkowski R, Sowa P, Pancewicz S, Moniuszko-Malinowska A. Alpha-gal syndrome: an emerging cause of food and drug allergy. *Clin Exp Allergy J Br Soc Allergy Clin Immunol*. 2020;50(8):894–903.
23. Hilger C, Fischer J, Swiontek K, Hentges F, Lehnert C, Eberlein B, et al. Two galactose- α -1,3-galactose carrying peptidases from pork kidney mediate anaphylactogenic responses in delayed meat allergy. *Allergy*. 2016;71(5):711–9.
24. Kwak M, Somerville C, Van Nunen S. A novel Australian tick Ixodes (Endopalpiger) australiensis inducing mammalian meat allergy after tick bite. *Asia Pac Allergy*. 2018;8(3): e31.
25. Commins SP. Diagnosis and management of alpha-gal syndrome: lessons from 2,500 patients. *Expert Rev Clin Immunol*. 2020;16(7):667–77.
26. Steinke JW, Platts-Mills TA, Commins SP. The alpha-gal story: lessons learned from connecting the dots. *J Allergy Clin Immunol*. 2015;135(3):589–96.
27. Westermann-Clark E, Pepper AN, Lockey RF. Economic considerations in the treatment of systemic allergic reactions. *J Asthma Allergy*. 2018;11:153–8.
28. Taylor BWP, Ratchford A, Van Nunen S, Burns B. Tick killing in situ before removal to prevent allergic and anaphylactic reactions in humans: a cross-sectional study. *Asia Pac Allergy*. 2019;9(2): e15.
29. Kaneko Y, Kitano S, Umayahara T, Kageyama R, Hashizume H. Tick anaphylaxis in Japan. *J Cutan Immunol Allergy*. 2019;2(2):53–4.
30. Dunkman WJ, Rycek W, Manning MW. What does a red meat allergy have to do with anesthesia? Perioperative management of alpha-gal syndrome. *Anesth Analg*. 2019;129(5):1242–8.
31. Wilson JM, McNamara CA, Platts-Mills TAE. IgE, α -gal and atherosclerosis. *Aging*. 2019;11(7):1900–2.
32. Wilson JM, Nguyen AT, Schuyler AJ, Commins SP, Taylor AM, Platts-Mills TAE, et al. IgE to the mammalian oligosaccharide galactose- α -1,3-galactose is associated with increased atheroma volume and plaques with unstable characteristics—brief report. *Arterioscler Thromb Vasc Biol*. 2018;38(7):1665–9.
33. Vernon ST, Kott KA, Hansen T, Finemore M, Baumgart KW, Bhindi R, et al. Immunoglobulin E sensitization to mammalian oligosaccharide galactose-a-1,3 (α -Gal) is associated with non-calcified plaque, obstructive coronary artery disease, and ST-segment-elevated myocardial infarction. *Arterioscler Thromb Vasc Biol*. 2022;42:352–61.
34. Rubin R. Red meat allergy associated with coronary artery plaque. *JAMA*. 2018;320(4):331–3.
35. Slayden TA, Shakir MKM, Hoang TD. A bull in a pill shop: alpha-gal allergy complicating treatment options for postprocedural hypothyroidism. *AACE Clin Case Rep*. 2020;6(3):e101–4.
36. Seddon I, Venincasa M, Farber N, Sridhar J. Alpha-gal syndrome in ophthalmology and medicine. *Int Ophthalmol Clin*. 2020;60(4):61–75.
37. Hawkins RB, Frischak HL, Kron IL, Ghanta RK. Premature bioprosthetic aortic valve degeneration associated with allergy to galactose-alpha-1,3-galactose. *J Card Surg*. 2016;31(7):446–8.
38. Muglia C, Kar I, Gong M, Hermes-DeSantis ER, Monteleone C. Anaphylaxis to medications containing meat byproducts in an alpha-gal sensitized individual. *J Allergy Clin Immunol Pract*. 2015;3(5):796–7.
39. Yuile A, Fanuli C, Van Nunen S, Diakos C, Clarke S, Steiner C, et al. Increased rates of cetuximab reactions in tick prevalent regions and a proposed protocol for risk mitigation. *Asia Pac J Clin Oncol*. 2021;17(6):448–53.
40. Raghavan RK, Koestel Z, Ierardi R, Peterson AT, Cobos ME. Climatic suitability of the eastern paralysis tick, Ixodes holocyclus, and its likely geographic distribution in the year 2050. *Sci Rep*. 2021;11(1):15330.