



Alpha-gal antibody due to Lone Star tick bite, a unique case of allergic reaction

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Introduction

Historically, antibodies to alpha-gal were initially diagnosed with administration of cetuximab. After further studying the chemical structure of cetuximab, it was found that approximately 30 % of the structure of cetuximab consisted of an oligosaccharide epitope, galactose- α -1,3-galactose (alpha-gal) [1]. Coincidentally, the high rate of allergic reactions also occurred in regions with the greatest incidence of Rocky Mountain spotted fever. It was later determined that the tick bite from *Amblyomma americanum* (Lone Star tick) carried the antigen, and when humans were bitten, their immune systems would mount immune responses against the alpha-gal component [2]. The immune response is type 2 helper T-cell (T_H2) driven with an immunoglobulin E (IgE) mediated activation against the alpha-gal allergen [3].

In the United States the *Amblyomma americanum* is the only vector that causes IgE response to alpha-gal. Other countries have different ticks that produce the IgE response. Australia has *Ixodes holocyclus* and various European countries have *Ixodes ricinus* [4]. This case presentation features an evolving additional diagnosis attached to an already well-known clinical condition associated with tick borne illnesses and emphasizes the primary care provider's role in identifying this condition for improved management.

Case report

The patient was a 47-year-old Caucasian male with no significant medical history. He was seen at his primary care physician's office for an annual examination and his only

medication was azelastine hydrochloride and fluticasone propionate, nasal suspension. Allergen history included penicillin G benzathine, which caused swelling, and codeine phosphate, which caused hallucinations. Otherwise, the patient denied a history of food allergies. He worked as a beekeeper and reported a history of bee stings with large local reaction without anaphylaxis for which he carried injectable epinephrine. During the visit, the patient voiced a concern of a tick bite earlier in the spring. He initially noted a tick bite on his left upper thigh, but promptly removed it within 24 h with no further treatment. Per the patient's history, he identified it as a Lone Star tick because of the "white markings on its back".

In the interim, he denied subjective or objective fever, nausea, rashes, joint swelling, or other systemic symptoms. He also reported sporadic episodes of nausea with non-bloody, non-bilious vomiting with no apparent sick contacts or changes to his diet other than his typical meals. He did not make a temporal connection at that time until it reoccurred several weeks later with dinner, and specifically a beef hamburger. He again experienced a similar episode after a meal of pasta with meat. He further noted, the previous summer, he traveled to Utah, and recalled eating hamburgers with subsequent nausea, vomiting, and, new-onset of hives roughly six to eight hours after that meal. At no point in time did the patient complain of shortness of breath or symptoms suggestive of anaphylaxis or airway compromise. Beyond the symptoms, he was able to continue his daily routine between symptom episodes.

Prior to his office visit, he discontinued eating all red meat products with no further symptomatic episodes. He was referred to an allergist, who performed an allergen antibody panel against pork, beef, garlic, and onion. Tryptase was negative and galactose alpha 1,3 galactose IgE was elevated (Table 1). Class provides interpretation of antibody results against pork, beef, garlic, and onion. Pork and beef were noted as class 3, which is "high level"

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Table 1
Allergen panel results.

Name	Value	Reference range
Pork (F26) IgE	5.65	Class 3
Beef (F27) IgE	6.87	Class 3
Garlic (F47) IgE	0.29	Class 0/1
Onion (F48) IgE	0.18	Class 0/1
Tryptase	2	< 11 ng/mL
Galactose Alpha 1,3 Galactose IgE	9.76	< 0.35 kU/L

Table 2
interpretation of IgE values based on class.

Specific IgE class	kU/L	Level of allergen Specific igE antibody
0	<0.10	Absent/undetectable
0/1	0.10–0.34	Very low level
1	0.35–0.69	Low level
2	0.70–3.49	Moderate level
3	3.50–17.4	High level
4	17.5–49.9	Very high level
5	50–100	Very high level
6	>100	Very high level

and garlic and onion were class 0/1, which is very low level (Table 2).

Initial complete blood count was significant for a white blood cell count of 3.6 with a normal differential. Absolutely neutrophil, lymphocytes, monocytes, and eosinophils were normal.

Conclusion

His reported tick bite was likely not the inciting bite. The patient's occupation likely predisposed him to tick bites during his fieldwork. Typical food allergies arise immediately after consumption; however, alpha-gal reactions time of onset can range from 3–6 hours after ingestion to weeks later [5]. The temporal relationship between meat ingestion and onset of an allergic reaction is patient driven. A close ear during a patient's history can help elucidate the possibility of a tick borne allergic reaction. Patient driven diagnoses are not new, and have been studied in other conditions including a recent 2016 study in the Journal of Joint Bone and Spine discussed the role of social media in diagnosing granulomatosis with polyangiitis (GPA). Flaherty et. al examined a subset of 28 patients to understand the eventual route to diagnosis at the University of North Carolina Allergy and Immunology clinic. Their study found that while six patients were diagnosed within one year of symptoms, the remaining patients average time to diagnosis was seven years. Prolonged time to diagnosis and symptoms inevitably lead to not only patient and family frustration, but also a significant amount of health care utility spent in the primary care office as well as acute care settings including urgent care and emergency departments [5]. Tick-borne induced red meat allergy is an emerging diagnosis. With this in mind, it is important to keep in mind that less commonly known consequences of tick borne illnesses to avoid potential misdiagnoses and shorten the time to diagnosis and adequate management.

Amblyomma americanum, which is the only vector in the United States that appears to cause IgE response to alpha-gal, also is known to transmit other infections. It also carries *Ehrlichia rickettsia* that cause ehrlichiosis and *Rickettsia spp.* that cause Rocky Mountain Spotted Fever. It is important to pay attention to patients who were recently diagnosed with either of these two conditions who now present with a sudden meat allergy or various gastrointestinal complaints [4].

In terms of management, ideally, serum IgE levels to alpha-gal can be drawn eight to 12 months to monitor levels. Treatment includes avoidance of further tick bites and no meat consumption for one to two years. Studies have shown if patients can follow prevention and avoidance measures, tolerance to red meats return within that time period. Equally important in making the diagnosis is advising patients for management and other complications. Advice for patients diagnosed with this type of allergic reaction includes complete cessation of non-primate mammalian meat including beef, pork, and lamb. Also, for patients with or without a history of asthma, alpha-gal allergy does not pre-dispose patients to new-onset of asthma or increase the risk of acute exacerbations, respectively [6].

It is important to consider additional precautions when dealing with patients who have an allergy to alpha-gal. Bioprosthetic heart valves are made from bovine or porcine and have shown to cause hypersensitivity reactions with possible accelerated degrading of the valves. Many medications (acetaminophen, lisinopril, and clonidine) and vaccines (influenza and zoster) are also known to contain alpha-gal [7]. Tick borne pathology now extends beyond the board basics of the well-known rash and heart block. Now, ticks are inducing allergic responses that are not typical of allergic responses. Delayed onset of hypersensitivity and an emerging diagnosis highlight the unique nature of the alpha-gal allergic reaction.

CRedit authorship contribution statement

Billy Zhang: Conceptualization, Writing - original draft, Writing - review & editing, Investigation. **Michael Hauk:** Writing - review & editing, Investigation. **James Clyne:** Writing - review & editing, Supervision.

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