

Delayed Anaphylaxis to Mammalian Meat: A Fascinating Disease and Captivating Story

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Abstract

Delayed anaphylaxis to mammalian meat is a newly recognized IgE-mediated syndrome associated with Lone Star tick bites. IgE-mediated anaphylaxis classically occurs within one hour of exposure to the allergen, which is typically a protein epitope. However, in this disease, circulating antibodies to a carbohydrate, alpha-gal (galactose-alpha-1,3-galactose), stimulate the anaphylactic cascade with hives, diarrhea, abdominal cramps, respiratory distress and anaphylactic shock developing after ingestion of beef, pork or lamb meat. The delayed onset of symptoms three to six hours after ingestion of meat is unique. Recognition and understanding of this disease is important for treating and educating patients with suggestive symptoms. Avoidance of red meat is the recommended therapy.

What Is It?

Delayed anaphylaxis to mammalian meat caused by tick bites is a newly recognized syndrome with a unique pathophysiology and clinical presentation. It was initially reported in the Southeastern U.S. (Tennessee, North Carolina, Arkansas, Missouri and Virginia).¹ Subsequent cases were more widespread and included cases in Texas, Georgia, South Carolina, Mississippi, Kentucky, Oklahoma, and West Virginia.^{1,2} Outside of the U.S., there have been cases reported in Australia, France, Germany, Sweden, Spain, Italy, Japan and Korea.³

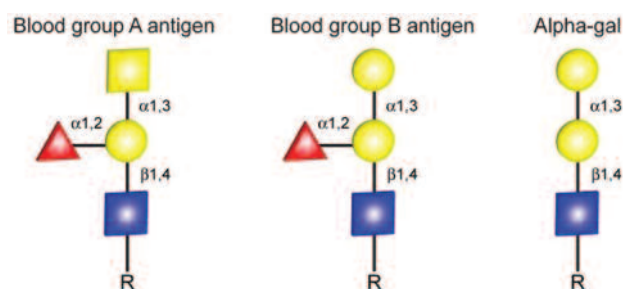
Anaphylaxis to mammalian meat is triggered by circulating IgE antibodies to the carbohydrate galactose-alpha-1,3-galactose (alpha-gal).⁴ These IgE antibodies in the U.S. are caused by bites of larval or adult Lone Star ticks (*Amblyomma americanum*) predominantly, if not exclusively.⁴ The IgE response with resultant histamine release is implicated in pathogenesis of the reaction.⁴

Patients with IgE alpha-gal antibodies develop hives, shortness of breath, angioedema, congestion and wheezing. Patients might report diarrhea and abdominal cramps, and could become hemodynamically unstable and develop anaphylactic shock three to six hours after ingestion of mammalian meat.² Patients commonly present after waking in the middle of the night with hives and

anaphylaxis after ingesting red meat for dinner.² Patients might report a history of exposure to tick bites with symptoms occurring after eating red meat, but not fish or poultry.⁴ A high suspicion and understanding of the epidemiology of the disease is imperative for diagnosis.² The diagnosis is confirmed using IgE immunoassays to galactose-alpha-1,3-galactose (alpha-gal), which are commercially available.⁵

Alpha-gal is a carbohydrate found on non-primate mammal and tick glycoproteins (Figure 1).^{6,2} Humans and higher primates cannot produce alpha-gal, which makes it possible to stimulate production of IgG antibodies to this oligosaccharide.⁴ Alpha-gal is a major transplantation barrier between primates and other mammals.⁴ Before

Figure 1. The structure of alpha gal compared to blood group A and B



identification of delayed anaphylaxis to red meat, it had not been known to cause IgE-mediated anaphylaxis.²

Avoidance of all mammalian meat (including beef, pork and lamb) is the current recommendation for alpha-gal sensitized patients. As anaphylaxis is potentially fatal; counseling and education about avoidance of tick exposure, in addition to equipping patients with an epinephrine auto injectors, is vital in management.²

Why is it Unique?

There are numerous unique and unusual aspects in the pathogenesis and clinical presentation of this syndrome. Adult-onset food allergy is rare, and patients with this disease report a history of ingestion of red meat for many years with no symptoms. In contrast to typical IgE-mediated anaphylaxis which occurs within one hour of allergen exposure, the anaphylaxis in this syndrome is delayed, with the IgE-mediated response to antibody alpha-gal occurs on average 3-6 hours after ingestion of alpha-gal containing meat. Interestingly, commercially available skin prick tests for mammalian meat are most often negative.⁴ Moreover, in classical food allergies (milk, egg, wheat, soy, peanut, tree nut, fish and shellfish), the major epitopes are known to be proteins. However, alpha-gal is unique, as it is a carbohydrate recognized by IgE antibodies.²

Discovery: Why is it Important to Report Cases and to Link Clues, Document Observations and Utilize Epidemiology?

The identification of the relationship between tick bites and meat allergy is as interesting and unique as is the disease itself. It is a story in which close observation, case reporting, the use of epidemiology and insightful analysis was essential in elucidating the disease process.

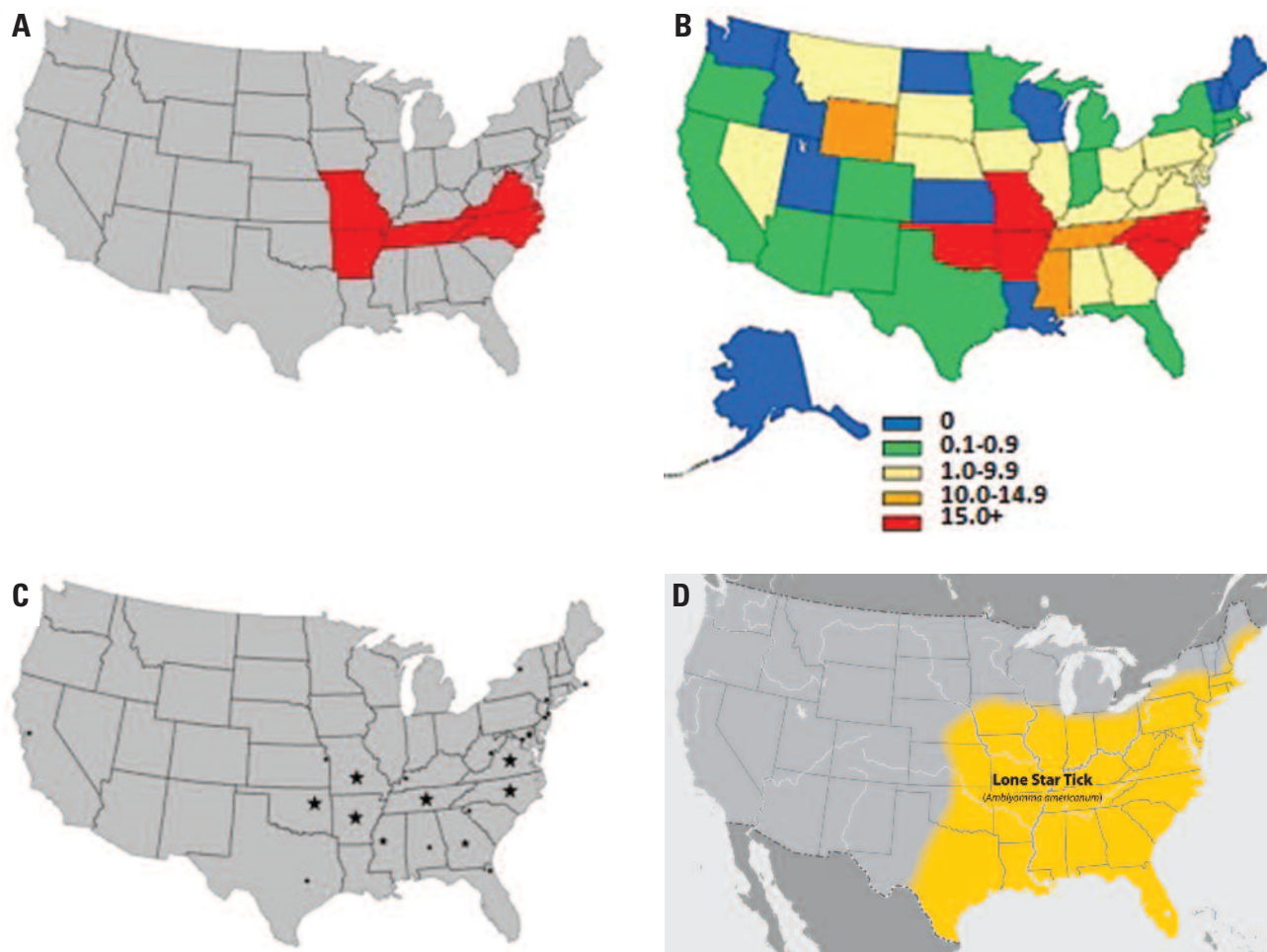
The story began in 2005, with an increased incidence of anaphylaxis in patients receiving cetuximab (a monoclonal antibody against epidermal growth factor receptor used for treating colorectal and head and neck cancers) was observed.⁷ Patients who developed anaphylaxis did so within minutes of receiving their first intravenous infusion of cetuximab. Interestingly, evidence of IgE antibodies against cetuximab was present before the first exposure to the medication.⁷ This IgE was specific for alpha-gal that was present on the Fab portion of the cetuximab heavy chain.⁷ Complicating this observation was the fact that alpha-gal is a carbohydrate found on non-primate mammal and tick glycoproteins, but is not made by humans.^{2,8} This carbohydrate had not been known to cause IgE-mediated anaphylaxis.² During monoclonal antibody

production using animal cell lines, oligosaccharides made by the animal cell attach to the antibody.² In theory, foreign oligosaccharides such as alpha-gal can cause an allergic reaction. However, such reactions were thought to be uncommon because humans typically make IgE antibodies against protein, not carbohydrate determinants.¹

Cases of cetuximab-associated anaphylaxis have been shown to have a geographic predominance in the southeastern U.S. (sensitization was as high as 20 percent in some states).⁷ Researchers have postulated that sensitization to alpha-gal in the Southeastern states has an association with tick bites since development of IgE alpha-gal seemed to follow tick bites in certain individuals.^{4,9} In fact, the geographic distribution of the cetuximab-induced anaphylaxis and reported delayed reactions to red meat correlate with the distribution of the Lone Star tick, (*Amblyomma americanum*), and match the maximum incidence of Rocky Mountain Spotted Fever which is transmitted by the same tick (Figure 2).^{1,2} In other countries, other tick species, such as *Ixodes ricinus* in Europe, and *Ixodes holocyclus* in Australia, have been implicated in the pathogenesis of meat allergy.⁴ However, *Ixodes scapularis*, the main vector of Lyme in the U.S., does not induce IgE to alpha-gal and is less likely to cause itching compared to the Lone Star tick.⁴ The Lone Star tick is much more aggressive in both adult and larvae forms than *Ixodes scapularis*.¹ The larvae tick (also called seed tick) bites are often confused with chiggers (larval form of the Trombiculid mite).^{1,3,4} Long attachment, repeated attachments, and large numbers of larvae bites are all contributing risk factors to development of anaphylaxis.^{1,3} The presence of alpha-gal has been found in the gastrointestinal tract of ticks, matching the staining pattern in sera of patients with IgE positive to alpha-gal.^{1,9}

The question of why this anaphylaxis emerged dramatically over the last few years remains unanswered. Although the exact mechanism is unknown, the epidemiological evidence in the U.S. would suggest that the rise in the deer population has played an important role.^{1,4} The exponential increase in lone star tick population parallels the increase in the deer population (a major carrier of these ticks in the U.S.) in the past 30 years.^{10,11} It was linked to the enactment of leash laws for dogs, a decrease in the number of hunters, and movement of the deer into suburban areas, which provide a means for the ticks to be transported over large geographic areas quickly.⁴

Figure 2. Comparison of the states where anaphylactic reactions to cetuximab were reported in 2006 (A) and the reported prevalence of Rocky Mountain spotted fever (B). Distribution of known cases of patients with delayed anaphylaxis to red meat whose serum contained IgE antibodies to alpha-gal (incidence rates per 1 million persons). (C). Markers indicate the number of cases (D), the known distribution of the tick *Amblyomma americanum* is shown: data from CDC.



Courtesy of Commins SP, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. *J Allergy Clin Immunol.* 2011;127(5):1286-93.e6.

Desensitization therapy for alpha-gal sensitive patients has been successful in the case of cancer patients requiring treatment with cetuximab, but to date, has not been accomplished in the case of meat-allergic patients.² Patients with this syndrome remain symptom free with avoidance of red meat, and report no symptoms with ingestion of non-mammalian meat such as turkey, fish or chicken.⁴ The long-term prognosis of this condition is not well described. However, it is thought that if a strict diet is followed, and tick re-exposure is avoided, reactions may lessen over time.^{12,13}

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