Anaphylaxis to the Carbohydrate Side Chain Alpha-gal

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KEYWORDS

• Delayed anaphylaxis • Alpha-gal • Ticks • Red-meat allergy • Cetuximab

KEY POINTS

- In 2007, the monoclonal antibody cetuximab was causing severe hypersensitivity reactions during the first infusion in a region of the southeastern United States.
- Investigation of pretreatment sera established that they contained immunoglobulin (Ig) E against the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal), which is present on the Fab of cetuximab.
- Alpha-gal is a blood group substance of nonprimate mammals.
- These IgE antibodies are also associated with delayed anaphylaxis to red meat (ie, to meat or organs of those animals that carry this oligosaccharide).
- There is now extensive evidence that the primary cause of these IgE antibodies is bites from the tick *Amblyomma americanum* or its larvae.

INTRODUCTION AND HISTORY

When Karl Landsteiner[1] first defined the ABO system, he also recognized a B-like substance on mammalian cells. At that time he reported that all immunocompetent individuals had agglutinating antibodies against this substance. Adsorption of these antibodies against rabbit red cells was part of the proof that rabbit cells can activate the alternate pathway of human complement.[2] This B-like substance is now known to be galactose-alpha-1,3-galactose (alpha-gal), which is structurally similar to the B blood group (**Fig. 1**).[3,4] This carbohydrate is a well-recognized immunologic barrier

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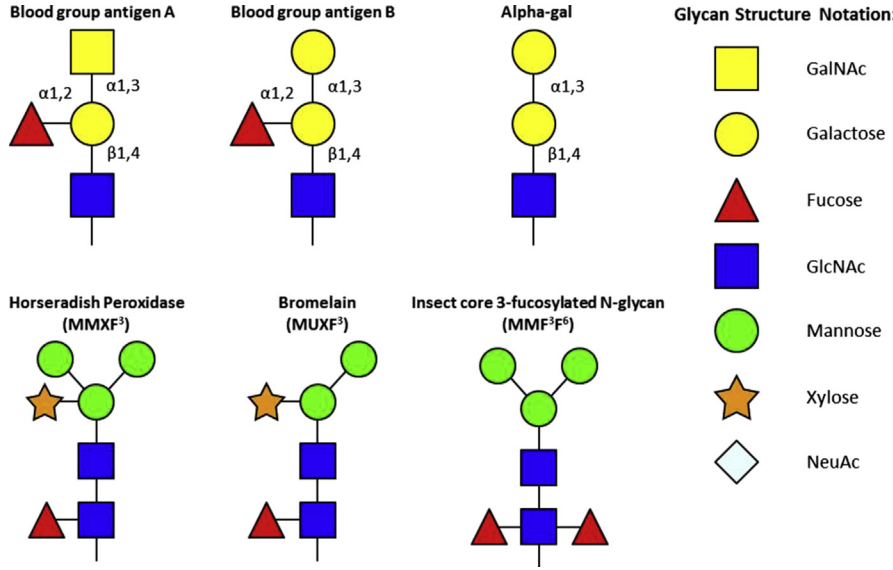


Fig. 1. Glycan structure of blood group antigens and alpha-gal contrasted with those of plant- or insect-related Cross reactive carbohydrate determinants. (*Adapted from* Commins SP, Platts-Mills TA. Anaphylaxis syndromes related to a new mammalian cross-reactive carbohydrate determinant. J Allergy Clin Immunol 2009;124(4):652–57.)

in xenotransplantation. Xenoreactive natural antibodies directed against the alpha-gal moieties on nonprimate mammalian tissue are often implicated in acute organ rejection. One way to circumvent this obstacle may be to raise transgenic organs in pig knockouts lacking the gene expressing alpha-(1,3)-galactosyl transferase, an enzyme inactivated in all primates.[5] It has also been suggested that the antibody response to alpha-gal is as much as 1% of the total immunoglobulin; however, more recent assays in our group suggest a low quantity of immunoglobulin (Ig) G antibodies.[6,7]

The story of IgE to alpha-gal starts in 2006 with 2 anaphylactic reactions to cetuximab in Bentonville, Arkansas, 1 of which was fatal. At the same time, there were 4 observations that were interesting but unexplained:

1. The monoclonal antibody (mAb) cetuximab was causing severe anaphylactic or urticarial reactions in up to 15% of patients treated in Tennessee and North Carolina but not in New York or Boston[8]
2. A patient aged 43 years reported 4 episodes of anaphylaxis, each of which started 4 hours after eating a hamburger (**Box 1**)
3. Sixty percent of the school children in a Kenyan village had serum IgE specific for cat extract, although there were no cats in the village and no relevant allergic symptoms[9]
4. The increasing deer population in rural and suburban Virginia had reached epidemic numbers

At that point, there was no reason to connect these observations and none of them made sense. Investigation of the specificity of the IgE present in the sera of patients before their first cetuximab treatment necessitated the development of an assay for IgE to cetuximab. This assay was simplified because a technique in which the target antigen was biotinylated and then bound to streptavidin ImmunoCAP (Phadia, Portage, MI) had been established in the previous year.[10] At that point, we were

Box 1
Delayed, or late night, anaphylaxis to red meat: the presentation and the clinical problem

1. For several years before 2008, patients were presenting to general medicine or allergy clinics for investigation of anaphylaxis or recurrent episodes of urticaria in which the cause was not obvious
2. The histories were striking for onset as an adult, presentation late at night, and/or no apparent acute cause (ie, no bites or stings, no medicines, and no foods within 3 hours of the episode)
3. Most cases had no history of conventional symptoms of food allergy; however, a significant proportion of the cases had made an association with eating beef, pork, or lamb earlier in the day
4. When the patients were tested using a prick test with commercial food extract, including beef, pork, or lamb, they had negative or very small responses (ie, wheals measuring 2–3 mm) to the meats
5. Because of the adult onset, long interval after eating, and negative prick skin tests, many or most of the patients were told they did not have food allergy; nonetheless, they had specific IgE for alpha-gal as well as beef, pork, and lamb

approached by Bristol Myers Squibb (BMS) to become involved with the investigation of the reactions to cetuximab.

INVESTIGATION OF THE REACTIONS TO CETUXIMAB: ESTABLISHING THAT THE ANTIGEN ON THAT MOLECULE IS GALACTOSE-ALPHA-1,3-GALACTOSE

The involvement with BMS brought with it connections to ImClone, who manufacture cetuximab, as well as to Dr Chung and the oncology group at Vanderbilt who had pretreatment sera from patients who had been treated with cetuximab. Many of the sera from Tennessee had IgE antibodies to cetuximab; however, an equal percentage of sera of controls from Tennessee had IgE specific for cetuximab. Thus, it was clear that the presence of these antibodies had everything to do with rural Tennessee and nothing to do with cancer. As an additional control, sera were assayed from a cohort of mothers in Boston (n = 341). In that group, only 1 serum had detectable IgE to cetuximab. Thus, in keeping with the known geographic distribution of reactions to cetuximab, there was good evidence that these antibodies were common in some southern states but rare in northern cities. Among the treated patients, the presence of IgE antibodies to cetuximab of greater than or equal to 0.35 IU/mL was strongly associated with severe reactions during the first infusion (odds ratio, 35).[11]

The next problem was to identify the specificity of the antibodies to this mAb, remembering that they were preexisting. Initially, a wide variety of known allergens including weeds, fungi, and also parasites were considered. Given that other mAbs did not give positive results with these sera it seemed possible that the epitope for these antibodies could be a posttranslational modification of the molecule related to the mouse cell line SP2.0 in which it is expressed. The solution of specificity became easier, because of 2 contributions from ImClone. They provided the same amino acid sequence as cetuximab expressed in Chinese hamster ovary (CHO) cells, a cell line that is not used for the commercial production of cetuximab and is known to produce different glycosylation. In addition, they published the details of the glycosylation of the commercially available cetuximab, which is expressed in a mouse cell line SP2.0.[12] These studies established that the sera with IgE antibodies to cetuximab did not bind to the same antibody expressed in CHO cells, and that the binding was

specific for the Fab portion of the molecule. It was Dr Beloo Mirakhur at BMS who first suggested that the target had to be alpha-gal. Full evidence for the specificity was obtained both from direct binding studies and inhibition studies.[11] The target of these IgE antibodies has now been confirmed from studies in Stockholm, Germany, and the Netherlands.[13–15] There is now no doubt that most of the severe reactions to cetuximab are a direct consequence of the presence of IgE to alpha-gal before the first infusion.[11,16]

FURTHER DEVELOPMENTS RELATED TO CETUXIMAB AND OTHER MONOCLONAL ANTIBODIES

In our initial publication, there was a simplistic image of the structure of cetuximab showing the glycosylation sites.[11] Over the next 2 years it became clear that this was not completely accurate. First, the sugars are complex, including diantennary and triantennary complex oligosaccharides with different expressions of alpha-gal (**Fig. 2**).[17] Second, there can be alpha-gal on the Fc portion of the molecule, and, third, in the normal structure of the Fc portion of IgG the glycosylation at Asn299 does not face outwards (see **Fig. 2**).[17,18] Dr Paul Parren and his group at Genmab in Utrecht used sera from Virginia to investigate the presence of relevant sugars on the Fc portion of cetuximab and infliximab. Those results confirmed our main finding that the alpha-gal, which could be identified on the whole molecule, was on the Fab portion of the heavy chain at Asn88. However, when the 2 chains of the Fc were separated using proteinase K there was detectable alpha-gal on the heavy chain.[15]

The combination of these results with other findings made it clear that the glycosylation site on the Fab at Asn88 is a problem, although this glycosylation is not thought to have a significant role in the activity of the molecule. Consequently, the glycosylation site on the Fab at Asn88 has been engineered out of the structure of most new mAbs. Thus, this specific problem is unlikely to arise again. The glycosylation on the Fc portion of IgG molecules plays an important role in defining the binding of IgG to different Fc receptors. It is now possible to engineer the expression of oligosaccharides on these antibodies so that the structure allows binding to different Fc receptors.[18]

DELAYED ANAPHYLAXIS TO RED MEAT

Once the assay for IgE to alpha-gal was established, sera from several different kinds of patients were screened. This screening included patients with histories of asthma, chronic urticaria, atopic dermatitis, and anaphylaxis. The most common history that correlated with IgE to alpha-gal was of urticarial or anaphylactic reactions occurring a few hours after eating red meat, beef, pork, or lamb (see **Box 1**), including the original case and also 2 members of our group. In 2009, we reported 24 cases, all of which had a typical history of delayed urticaria or anaphylaxis and had IgE specific for alpha-gal.[19] In that same year, it was confirmed that the oligosaccharide that Dr Van Hage and her colleagues[20,21] in Sweden had previously identified as an IgE binding epitope on cat IgA was also alpha-gal.

By 2011, about 400 cases of delayed urticaria or anaphylaxis to red meat were known and we evaluated symptoms, lung function, exhaled NO, and serum IgE on ~200 patients. The resulting evidence showed that IgE to alpha-gal had no association with asthma.[22] Thus even patients with high-titer IgE to alpha-gal living in a house with a cat had no increase in their risk of asthma. This finding was surprising because cats, like all mammals, have alpha-gal on many of their proteins and lipids. In contrast, using an assay for alpha-gal, we were not able to detect this antigen airborne in homes

with a cat even in the presence of high Fel d 1 levels.[22,23] The studies at that time also examined sera from the Kenyan village and established that the IgE to cat that had been observed earlier was explained by IgE to alpha-gal.[9,22] A recent report on patients in Zimbabwe found that IgE antibodies to alpha-gal were common among patients being evaluated in an allergy clinic.[24] In contrast, the results from Africa have not so far identified cases of meat allergy.

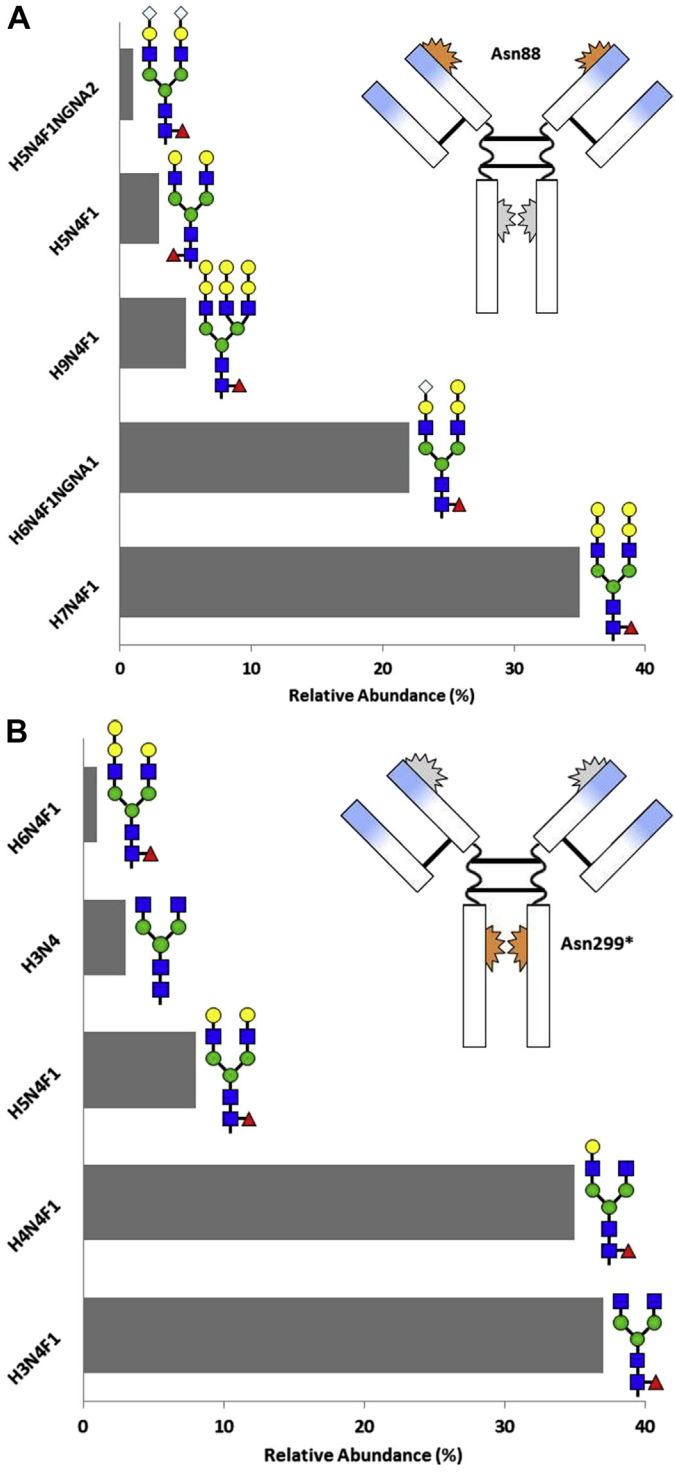
Anaphylactic or urticarial reactions to red meat are well recognized in Australia,[25] which came to light from the original observations of Dr Sherril Van Nunen. In 2006, she had reported to the New South Wales Allergy Society that individuals who had experienced tick bites in the bush were at risk of serious reactions following ingestion of red meat. She published her results in 2009 and related those results to the published evidence about IgE to alpha-gal.[11,19,25] Subsequently, with Dr Mullins we confirmed that the patients with delayed reactions to red meat in Australia had IgE antibodies specific for alpha-gal.[26] Cases of reactions to red meat have now been identified in France, Sweden, Germany, Japan, and Australia as well as in the United States (**Fig. 3**A, **Table 1**).[27–34]

THE EVIDENCE THAT TICKS PLAY AN IMPORTANT ROLE AND ARE POSSIBLY THE ONLY SIGNIFICANT CAUSE OF IMMUNOGLOBULIN E RESPONSES TO GALACTOSE-ALPHA-1,3-GALACTOSE IN THE UNITED STATES

The speed with which new cases of delayed anaphylaxis to red meat (DARM) have been diagnosed in the United States strongly suggests that the condition has increased over the last 10 years. Although it is difficult to prove that a disease that was not previously recognized has increased, the reintroduction of deer to the east coast and the subsequent dramatic increase in the deer population provides a possible explanation for the increase in cases. The white-tailed, or Virginia, deer (*Odocoileus virginianus*), which nearly became extinct in large areas of the east coast in 1930, is a major host for ticks. These deer were reintroduced to the Blue Ridge Mountains around 1950, and their numbers have been increasing rapidly since then. Thus it is plausible that the dramatic increase in the deer population, particularly close to residential areas, has played a major role in increasing exposure to the lone star tick and its larvae.[35]

The initial reason for suspecting tick bites in the United States was that the areas of the 2 diseases associated with IgE to alpha-gal seemed to be similar to the area with maximum incidence of Rocky Mountain spotted fever.[36–38] That disease is transmitted by 2 species of ticks: *Dermacentor variabilis* (the brown dog tick) and *Amblyomma americanum* (the lone star tick) (see **Fig. 3**B, **Table 2**). The lone star tick has been spreading rapidly in the United States and is being followed by the US Centers for Disease Control and Prevention because it is the major vector for ehrlichiosis.[36,37]

The evidence for tick bites as a major cause of IgE to alpha-gal comes from several observations (**Box 2**). First, we have documented increases in IgE antibodies after tick bites in 4 subjects. Second, there is a significant correlation between reports of prolonged itching after tick bites and the presence of IgE antibodies to alpha-gal in the serum. Bites of larval lone star ticks, like adult ticks, can be intensely pruritic. Bites from the deer tick *Ixodes scapularis*, which transmits Lyme disease, do not generally induce a pruritic skin response; itching after tick bites has been associated with a decrease in the risk of developing positive Lyme serology.[39] Third, there is an excellent correlation between IgE to alpha-gal and IgE to extract of the lone star tick ($r = 0.75$; $P<.001$).[38] In addition, evidence from the group in Stockholm showing the presence of alpha-gal in the gut of the tick and a similar correlation with tick bites in southern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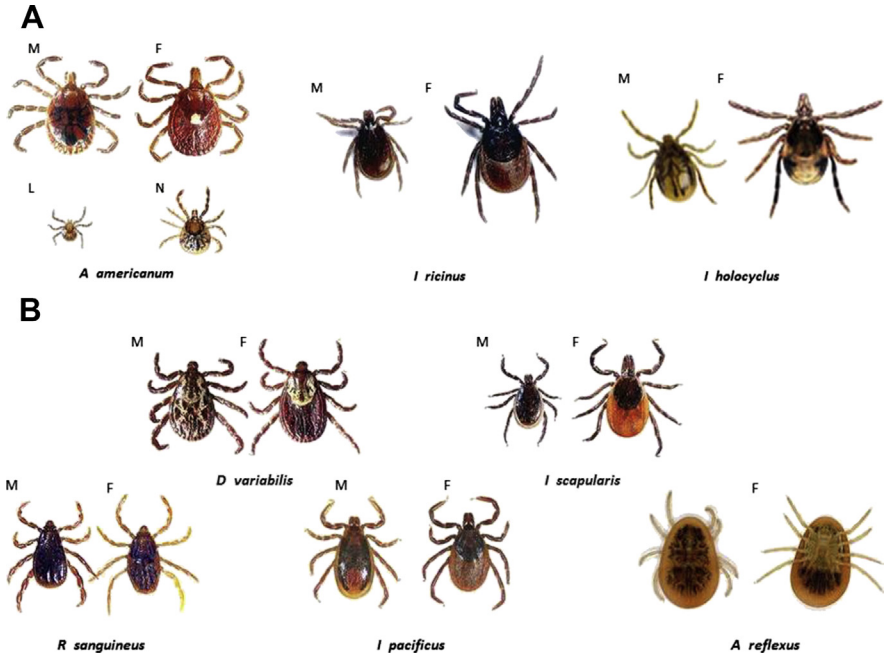

Fig. 3. (*A*) Tick species in which bites are associated with IgE response to alpha-gal. (*B*) Tick species associated with common tick-borne diseases or tick bite anaphylaxis. *A reflexus*, *Argas reflexus*; F, female; L, larva; M, male; N, nymph; *R*, *Rhipicephalus*. (Images of A americanum, D variabilis, I scapularius, R sanguineus, and I pacificus courtesy of University of Rhode Island TickEncounter Resource Center, http://www.tickencounter.org/; with permission.)

Sweden[33] has strengthened this correlation. In addition, subjects living in areas void of ticks do not have IgE to alpha-gal.[11,22,33] The lone star tick is the only tick in the United States whose larvae bite humans, and in several cases we have found high-titer IgE antibodies to alpha-gal following bites from larval ticks. These larval ticks are often known as seed ticks or chiggers. Given the evidence of bites of the lone star tick giving rise to this IgE response, the question becomes why does this tick give rise to such dramatic IgE responses and why are they directed at this oligosaccharide? The problem is in understanding whether this response has more in common with other responses to oligosaccharides (which are usually IgM) or with IgE responses to proteins. There is increasing evidence that the skin can be an important route for IgE antibody responses to proteins such as peanut and wheat.[40,41] However, with those antigens neither the route through which it enters the skin nor the time frame from exposure to antibody response is known.

Fig. 2. Relative abundance of glycosylation patterns on cetuximab at sites Asn88 (*A*) and Asn299 (*B*) as resolved by mass spectroscopy. The blue sections on the Fab arms indicate the murine segments of the antibody. (*Asterisk*) Alpha-gal is not exposed in the intact molecule. See **Fig. 1** for glycan structure notation. (*Adapted from* Ayoub D, Jabs W, Resemann A, et al. Correct primary structure assessment and extensive glyco-profiling of cetuximab by a combination of intact, middle-up, middle-down and bottom-up ESI and MALDI mass spectrometry techniques. MAbs 2013;5(5):699–710.)

Table 1
Countries where tick bites are associated with IgE responses to alpha-gal

Country	Tick Species	Cases	Food Reaction	Reference
Australia	*Ixodes holocyclus*	+400	Beef, lamb, pork, kangaroo, goat, venison, rabbit, horse, gelatin	25,26
United States	*Amblyomma americanum*	>1000	Beef, lamb, pork, venison, cow's milk, squirrel/road kill	19,22
France	—	20	Beef, veal, lamb, pork kidney, cow's milk, rabbit, horse	27,28
Spain	*Ixodes ricinus*	5	Beef, lamb, pork, rabbit	29
Japan	—	29	Beef, pork	30
Germany	*I ricinus*	60	Beef, lamb, pork kidney, gelatin	14,31,32
Sweden	*I ricinus*	40	Beef, pork, cow's milk, moose	33
Central America	*Amblyomma cajennense*	4	Mammalian meat	34

MONITORED CHALLENGES USING MAMMALIAN MEAT IN PATIENTS WITH DELAYED ANAPHYLAXIS OR URTICARIA TO RED MEAT

The nature of delayed anaphylaxis creates problems for any investigational or diagnostic challenge procedure. It is not feasible to perform either graded challenges or placebo-controlled challenges to investigate reactions that can take up to 6 hours. Our protocol involves a single dose of meat product and most of these studies were performed on patients who reported delayed episodes of urticaria. The potential risk of more severe reactions (eg, anaphylaxis) presents an additional layer of difficulty to diagnostic challenges because most patients are male in an age range in which creating a risk of anaphylaxis or the need for epinephrine is not appropriate. Accordingly, the studies were not performed on patients who reported previous episodes of anaphylaxis and were restricted to subjects less than 50 years of age in order to reduce the risk of the reactions or the use of epinephrine.[32,42]

Table 2
Causal organisms and tick species involved with the transmission of common tick-borne diseases or the less common tick bite anaphylaxis

Tick-borne Disease	Causal Organism	Implicated Tick
Lyme disease	*Borrelia burgdorferi* (United States) *Borrelia afzelii* and *Borrelia garinii* (Europe)	*Ixodes scapularis* and other *Ixodes* spp
Rocky Mountain spotted fever	*Rickettsia rickettsii*	*D variabilis*, *Rhipicephalus sanguineus*, *A americanum*
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*A americanum*
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes* spp
Anaphylaxis caused by tick bites	Tick saliva	*Argas reflexus* (Europe) *Ixodes holocyclus* (Australia) *R sanguineus* (Brazil) *Ixodes pacificus* (United States)

Box 2
Evidence that tick bites are a cause, or the major cause, of IgE responses to alpha-gal

1. The area of the United States where the IgE antibodies are common coincides with the distribution of the lone star tick
2. A large proportion of patients with these antibodies report prolonged itching after tick bites
3. In 4 cases we have followed increases in IgE antibodies to alpha-gal after tick bites
4. IgE to alpha-gal correlates strongly with IgE to extract of the lone star tick
5. In other countries, bites of ticks of other species have been associated with IgE to alpha-gal
6. Among populations living in large cities of the United States or the extreme north of Sweden where ticks are not present, IgE antibodies to alpha-gal are absent

IgE antibodies to alpha-gal can be measured with cetuximab on a streptavidin Immuno CAP (see Ref.[10]). The assay is also available commercially from IBT/Viracor (Lee's Summit, MO).

Monitored challenges have now been reported from France, Germany, and the United States.[28,32,42] Our challenge results involved 12 cases and 13 controls (**Table 3**). In 10 cases, there was a significant clinical response involving the skin and, in 1 of these cases, severe intestinal spasms as well. Three of the cases had an increase of serum tryptase level at the time of the skin reaction (ie, 2.5 to 5 hours after eating meat). All the patients who developed urticaria received antihistamines and in 2 cases the symptoms required epinephrine.[42] None of the controls had any symptoms and none of them received any treatment.

To investigate the mechanism of the delayed reaction, we also monitored patients' basophil levels during the challenge to investigate the activation of these cells as judged by upregulation of CD63. For the basophil studies the cells were fixed ex vivo without further stimulation. Ten of the alpha-gal IgE-positive subjects had significant upregulation of CD63 starting at 3 hours or later, which broadly correlated with the timing of the skin reactions. Surprisingly, 5 of the 13 controls showed significant upregulation of CD63 ex vivo at the same time (ie, 3–5 hours after eating meat).[42] We assumed that this upregulation reflects the time at which significant alpha-gal

Table 3
Red meat challenges in patients with or without IgE specific for alpha-gal

Group	Time to Symptoms (h)	Urticaria[a]	Treatment			Tryptase Level Increase
			Antihistamine	Epinephrine	Prednisone	
Allergic (n = 12)	2.45–5.00	10 of 12[b]	9 of 12	2 of 12	4 of 12	3 of 11[c]
Controls (n = 13)	NR	0 of 13[d]	0 of 13	0 of 13	0 of 13	0 of 13

Abbreviation: NR, not reported.
[a] Urticaria was characterized by flushing.
[b] Flushing with intestinal spasms was observed in only 1 of these subjects.
[c] Tryptase level increase: (1) 4.7 to 10.7 ng/mL, (2) 4.2 to 20.1 ng/mL, (3) 6.2 to 18.3 ng/mL.
[d] $P<.001$.

Data from Commins SP, James H, Stevens W, 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;134:108–15.

enters the circulation. However, there is published evidence that basophils have a receptor for very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) that can trigger histamine release.[43,44] Our current hypothesis is that the delay in the clinical response is best explained by the time needed for absorption of lipids and glycolipids as chylomicrons and the subsequent processing to VLDL and LDL.

In the Alsace region of France and the north eastern region of Germany, 2 separate groups have described cases of DARM.[27,28,31,32] In both areas they have identified pork kidney as an important cause of the naturally occurring reactions as well as an excellent agent for inducing reactions in the context of diagnostic challenges. In each case, the reactions were more severe and also more rapid with the kidney challenge. However, even with pork kidney none of the patients reported immediate (ie, within 20 minutes) oral symptoms.

A large proportion of patients report that their responses are not only delayed but that they are also inconsistent. Some patients report that responses occur more consistently if they take alcohol at the same time as the meat. Recently, the Biedermann group in Germany also reported that the response to pork kidney can be enhanced with exercise, aspirin, and/or alcohol.[32] The important question at this point is to establish what form of the glycolipid enters the circulation 2 to 5 hours after eating mammalian meat or organs, such as kidney, heart, stomach, or liver from nonprimate mammals.

SUMMARY

Two different and novel forms of anaphylaxis have now been associated with IgE to alpha-gal. Reactions to cetuximab continue to occur, including a fatal reaction that occurred during the first infusion in a 40-year-old patient with colon cancer in August of 2014.[11,16] In addition, severe delayed anaphylactic reactions to red meat continue to occur in patients who were not aware of being allergic, or had been dismissed by a physician because the physician did not think that the reactions could take 4 hours. In 2014, we reported a case of severe anaphylaxis to pork in a previously nonatopic 73-year-old woman.[45]

The characteristic features of the syndrome of DARM are late onset of urticarial or anaphylactic episodes, together with no immediate cause, a history of pruritic tick bites, and exposure to red meat 3 to 5 hours before the onset of symptoms. However, many cases are less obvious, with longer delays, no clear history of tick bites and symptoms such as gastrointestinal spasm alone, or just facial swelling. In some areas of the United States it is normal practice to test otherwise unexplained cases of anaphylaxis. In central Virginia IgE to alpha-gal is now the most common cause of anaphylaxis in adults. Among city dwellers the syndrome is rare, but nonetheless the syndrome needs to be on the list of possible causes of otherwise unexplained anaphylaxis.

The evidence about ticks as a cause of the IgE response is good but does not exclude a role for other parasitic exposures. Ticks in other countries are not the same. In Australia the relevant tick is *Ixodes holocyclus*, whereas in Europe the relevant tick is *Ixodes ricinus* (see **Fig. 3**). The group of investigators in Stockholm has shown that *I ricinus* has alpha-gal in its gastrointestinal tract.[13] In our experience, alpha-gal IgE titers seem to diminish over time with avoidance of ticks, although there is neither a regular time course for this loss of sensitivity nor a guaranteed reduction in symptom severity among all patients. In contrast, continued exposure to ticks seems to augment the already existing IgE antibody response. The important question is how these ticks induce an IgE responses and why it is directed against this specific oligosaccharide.

Table 4
Allergic diseases in which the route of sensitization is not the same as the route of exposure giving symptoms

Allergic Syndrome	Presentation	Route of Sensitization	Mechanism
Oral allergy syndrome	Oral symptoms; eg, to apple, cherries, hazelnut	Sensitization to inhaled pollen; eg, birch	Cross reactivity between Bet v 1 and major allergens; eg, Mal d 1, Pru av 1, Cor a 1
Pork/cat syndrome	Oral symptoms and anaphylaxis to pork	Sensitization to cat albumin (Fel d 2)	Cross reactivity between albumins of cat and pork
Peanut allergy	Anaphylactic reactions to oral peanut	Sensitization through the skin in patients with a filaggrin defect	Sensitization to Ara h 1 and Ara h 2
DARM	Delayed urticarial and anaphylactic reactions to red meat	Sensitization to alpha-gal from tick bites	Sensitization to mammalian oligosaccharide alpha-gal

One of the striking things about the syndrome is that the route of exposure to the antigen is via the skin, whereas the symptoms follow oral exposure. This difference adds to an increasing list of allergic diseases in which the route of initial exposure is not the same as the site of the symptoms (**Table 4**). In addition, the delay in reaction after eating meat adds to the group of conditions in which oral exposure seems to be causal and IgE antibodies are involved but the patient cannot identify the relevant food or food groups via more immediate, oral symptoms (ie, pruritus or swelling).[41,46,47] None of these conditions can be evaluated using double-blind placebo-controlled challenges.

The evolution in understanding of DARM has important implications in understanding and treating IgE-mediated hypersensitivity. No feature of the disease was obvious to allergists in practice, including to those who now study it. Most adult patients who reported reactions occurring 4 hours or more after eating meat and had negative or very small prick test responses to the relevant meat were informed that this could not be IgE-mediated hypersensitivity to the food. Furthermore, histories that included previous tick bites were thought to be irrelevant. In addition, the role of the increasing deer population in suburban areas of the east coast focuses attention on the many ways in which changes in human behavior have affected allergic disease.

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