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Food allergy to the carbohydrate galactose-alpha-1,3-galactose (alpha-gal): four case reports and a review

Until recently, food allergies to mammalian meats have been considered to be very rare. The observation that patients not previously exposed to the monoclonal chimeric antibody cetuximab suffered from severe anaphylaxis upon first exposure, led to the identification of galactose-alpha-1,3-galactose as a new relevant carbohydrate allergen. These patients later often suffered from anaphylactic reactions to red meat. Epidemiological data indicated that bites by the tick *Amblyomma americanum* in the USA, later also by *Ixodes* species in other continents, resulted in sensitisation to alpha-gal. On the other hand, in African patients with parasitic disorders, a high prevalence of anti-alpha-gal IgE, without clinical relevance, has been reported. In our four cases, one patient with a late onset of meat allergy had a history of a tick bite. The other three patients had symptoms from childhood or at a juvenile age. This indicates that in some patients, other ways of sensitisation may also take place. However, in patients without atopy, tick bite-induced IgE to alpha-gal may be more relevant. Diagnosis is based on a history of delayed onset of anaphylaxis. Skin tests with commercially available meat test solutions are often equivocal or negative; skin tests with raw meat and particularly pork kidney are more sensitive. Determination of specific IgE to alpha-gal is commercially available. The highest sensitivity is observed with skin and basophil activation tests with cetuximab which is, however, limited by its high costs.

Key words: food allergy, red meat, alpha-gal, delayed anaphylaxis

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Allergic reactions to foods are common. In particular, plant-derived food allergies are mostly based on cross-reactivity to allergens in pollen and frequently result in local reactions, such as the oral allergy syndrome, and more rarely in systemic allergic reactions and anaphylaxis. Allergic reactions to animal-derived food, such as milk and eggs, are rarely based on cross-reactive IgE and are particularly common in children and rarer in adults, whereas allergic reactions to seafood and fish, associated with systemic allergic reactions, are not uncommon in adults. They may be based on cross-reactive allergens, such as tropomyosine.

Until recent years, allergic reactions to mammalian meats have been considered to be extremely rare. During the last ten years, however, an increasing number of adult and paediatric cases has been reported, mostly from Western countries. These severe hypersensitivity reactions to mammalian meats have been traced back to a carbohydrate antigen, the galactose-alpha-1,3-galactose (alpha-gal) [1]. It is expressed in all mammals, except in humans and Old World monkeys [2], and also not *e.g.* in poultry, seafood, and fish. First reports of this new clinical entity originate from the group of Thomas Platts-Mills and colleagues in the USA [3, 4].

Their observation that patients who have been exposed for the first time to the monoclonal antibody cetuximab for

cancer treatment and who reacted upon this first exposure with severe anaphylaxis led to further investigations. It was then realised that many of these patients later also reacted to the ingestion of red meat. The more frequent occurrence of cases in the Southeastern states and epidemiological analysis [5] suggested a correlation to tick bites, particularly if severe and persistent local reactions had occurred. It is not clear how the tick bites induce specific IgE (sIgE) reactivity to alpha-gal. A correlation with multiple bites and persistent local reactions has been reported. It appears that individuals with blood group B are more prone to becoming sensitized [6]. Finally, in studies on African patients with parasitic disorders, a high prevalence of alpha-gal IgE and sensitization to cat allergens without clinical relevance has been observed [7].

Galactose-alpha-1,3-galactose (alpha-gal)

At the beginning of the last century, Karl Landsteiner already recognised that a B-like substance was present on mammalian cells, while working on the investigation of the human AB0 blood group system [8]. It was later recognised

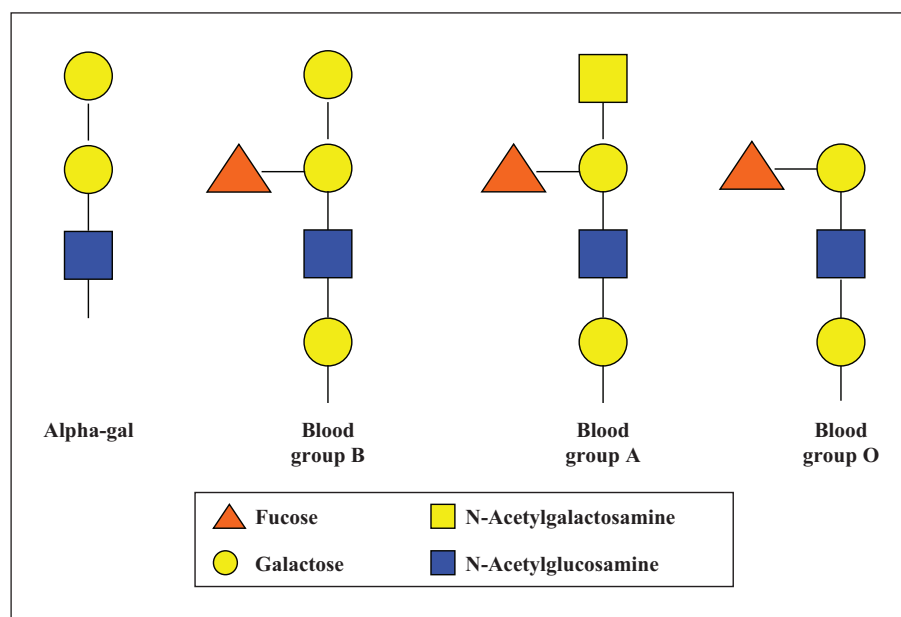


Figure 1. Glycan structures of human blood groups and alpha-gal (modified from Platts-Mills *et al.* [8]).

that this substance is alpha-gal, which has a similar structure to blood group B antigen (*figure 1*). It was later reported that IgG antibodies against alpha-gal are abundant in humans, but that also the isotypes IgM and IgA are present [9]. However, this high concentration of IgG to alpha-gal has been recently disputed and a lower quantity of anti-alpha gal IgG has been postulated. Still, these xenoreactive natural antibodies represent the major obstacle to xenotransplantation [8, 9]. It is, however, considered that they could be beneficially used, *e.g.* in cancer vaccines [9].

In humans and Old World monkeys, the enzyme responsible for the formation of alpha-gal, beta-galactosyl alpha-1,3-galactosyltransferase, is inactivated, allowing the production of anti-gal IgG and other isotypes to foreign antigens, whereas in other mammals it is still active. This inactivation is estimated to have happened several million years ago. Hypothetically, the presence of such anti-alpha-gal antibodies could have been an evolutionary advantage, since similar antigens are found on bacteria, viruses, and parasites [9].

When comparing blood group antigens A and B with alpha-gal, it is evident that there is a high similarity, particularly between the structure of blood group B and alpha-gal (*figure 1*) [6]. It is therefore interesting that particularly individuals with blood group B, who are most often rhesus negative, are more prone to sensitization to alpha-gal [10].

Cetuximab-induced hypersensitivity reactions

In 2004, the monoclonal chimeric antibody cetuximab (Erbix[®]) was studied in clinical trials for the treatment of metastatic colorectal cancers. In these early studies, a considerable number of patients (up to 15%) reacted upon

first exposure with severe and sometimes fatal anaphylaxis. These occurred mostly in patients living in the southeast of the USA, but less in patients living on the coast in the USA. In these former patients, it was later demonstrated that an IgE antibody to the carbohydrate alpha-gal was present [3]. Glycosylation of proteins is a posttranscriptional modification of the molecule and may play a major role in protein folding, stability, and adhesion. It is therefore critical for the function of proteins, including half-life and efficacy of, for example, monoclonal antibodies [11]. Cetuximab is produced in a murine myeloma cell line which has the capability to synthesize alpha-gal, where this posttranscriptional modification of the molecule takes place. It was later recognised that alpha-gal is present in abundance on cetuximab at the Fab end, and to a lesser extent on the Fc portion of the monoclonal antibody [5]. The Fab part of cetuximab, where alpha-gal is present, is an ideal position to bridge between pre-existing IgE bound on mast cells and basophils (*figure 2*). It was also shown that the same glycosylation

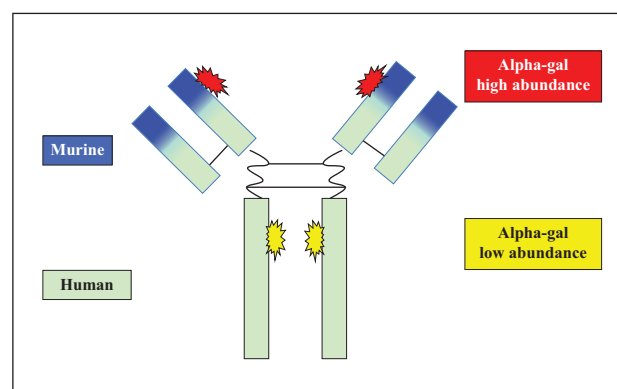


Figure 2. Structure of Cetuximab (Erbix[®]) (modified from Platts-Mills *et al.* [8]).

pattern may occur when Chinese hamster ovary cells are used [11]. For other chimeric monoclonal antibodies, such as rituximab and infliximab, however, this glycosylation with alpha-gal on the Fab part is not present.

Allergic reactions to red meat

An early study in the French literature reported a so-called “pork-cat-syndrome” or crossed allergy between pork meat and sensitization to cat epithelia [12]. Still, allergy to red meat has been considered an exceptional rarity until about 10 years ago, when more cases were identified, particularly in the midwest states of the USA [3, 4, 13]. However, it was quite surprising that most of these reactions occurred several hours only after the intake of meat, as opposed to the common observation of food-related anaphylaxis, which occurs usually within the first minutes to one to two hours. Symptoms included the whole range of symptoms, such as urticaria, angioedema, gastrointestinal disturbances, bronchospasm, and anaphylactic shock. The different types of meats included mainly pork, beef, lamb and venison, and often innards, such as kidney and liver. In some patients, cofactors such as exercise and alcohol were contributing.

In the meantime, an increasing number of cases have been reported, over 1,000 cases from the USA [8], ~400 from Australia [14], but also cases from different European countries, including Germany, France, and Switzerland [15-17]. Also, in Asian countries, an increasing number of cases have been identified [18-20]. In a paediatric cohort of 51 children with recurrent allergic symptoms starting with a delay of several hours after food intake, a high prevalence (88%) of sIgE to alpha-gal has been found. High sIgE was present in response to mammalian meat, whole cat and milk extract, but not to the specific components Fel d 1, casein, and other milk allergens, indicating cross-reactivity to alpha-gal present in the whole extracts but not to specific components [13].

Association with tick bites

From epidemiological data, it was postulated that in southeastern USA, bites particularly from *Amblyomma americanum* (lone star tick), could be responsible; in a further study there was an indication that particularly patients who had had a severe, persistent local reaction after a tick bite were more likely to develop IgE antibodies against alpha-gal [21]. Serological conversion to alpha-gal takes several months. In addition IgE reactivity to other mammalian meats and milk were also found.

This observation has also been made in patients from Australia and Sweden [22], indicating that also other ticks, such as *Ixodes ricinus*, could be responsible for the induction of IgE towards alpha-gal. In a Swedish study, there was evidence of the presence of alpha-gal in the gastrointestinal tract of *Ixodes ricinus*, supporting this hypothesis [22].

In view of the very frequent exposure to ticks, anaphylaxis from tick bites itself appears to be extremely rare. The first cases from *Ixodes holocyclus* date back to the 1940s and

1960, both from Australia, followed by some other cases [14]. Few reports have been published from other areas; *Ixodes pacificus* from California and *Ixodes ricinus* from Spain [14, 23, 24].

A recent study from Europe (Denmark and Spain) showed that the prevalence of sIgE to alpha-gal in the general population ($n=2741$) is about 2% ($n=52$) with specific IgE to alpha-gal (>0.35 - 0.70 kU/L) in 20, and >0.70 kU/L in 32 individuals (range: 0.72 - 119 kU/L). An association with tick bites, atopy, and cat ownership was clearly present [25]. In high-risk populations for tick exposure, such as forest workers and hunters, the sensitization rate may be considerably higher.

Alpha-gal in cat dander extracts and parasitic infestations

In an early publication, the association between a positive prick test to cat and anaphylaxis to pork led to the term “pork-cat syndrome”, and cross-reactivity to cat albumin has been postulated [12]. In a study on prevalence [25], an association between alpha-gal sensitization and cat ownership was identified. Based on further analysis of the homes of such patients, the presence of high Fel d 1 levels was found, albeit without asthmatic symptoms. There was no sensitization to Fel d 1 (cat secretoglobulin), but cross-reactivity among sIgE to alpha-gal and Fel d 5 (cat IgA) was identified. This antibody is also glycosylated with alpha-gal and may therefore induce sIgE and cross-react in cat dander extracts. For example, in children from a Kenyan village with high prevalence of parasitic disorders where no cat exposure took place, a high prevalence of sIgE to alpha-gal, but low prevalence of sIgE to Fel d 1, was identified [26]. This has been further confirmed, with many patients testing positive for skin tests to cat allergens, but without any respiratory symptoms, such as rhinitis or asthma. Alpha-gal is not airborne or present in house dust, therefore no asthmatic symptoms occur in sensitized patients [26].

In a study on parasite-infested African patients (Schistosoma, helminths) compared to African patients with cat allergy, a high prevalence of sIgE to alpha-gal (85%) and Fel d 5 (66%), but low prevalence to Fel d 1, was identified in the former. The patients did not have any allergic symptoms to food, indicating that sensitization to alpha-gal does not automatically lead to clinical manifestations. However, in such patients, the diagnosis of parasitic infestations may also be hampered [7]. In studies from Europe and USA, where parasitic infestations are rare, sIgE to alpha-gal was prevalent in tick-infested areas, but not in areas with low tick prevalence [8, 21, 25].

Occurrence of alpha-gal

It has been recently shown that in beef meat, several IgE-reactive proteins containing alpha-gal are present [27], four of which are stable to heat treatment. However, IgE to other non-alpha-gal containing proteins in meat allergic patients also exists, demonstrating that other IgE-specific moieties exist.

Gelatin is an ingredient of some processed foods, as gelatin colloids [4], as well as a stabilizing agent in some vaccines [28]. It is a potential alpha-gal containing allergen [29]. In few patients, reactions to gelatins after ingestion of sweet gums (*e.g.* Haribo®), again with a delayed onset, have been observed [30]. Also, reactions after vaccines and infusion of gelatin-containing volume expanders, confirmed by challenge tests, have been reported [29]. Alpha-gal was detected in gelatin colloids (Gelofusine, Haemaccel), in beef thyroglobulin, and in heavy cream. In contrast, no alpha-gal was detected in cow's milk (skimmed, or 1% or 2% milk fat) or fish gelatin. Cetuximab, on the other hand, contains a high concentration of alpha-gal epitopes.

Diagnosis of allergic reactions to red meats

Due to the fact that the anaphylactic reactions to red meat typically occur after a delay of several hours, in the past, many of these patients might have been missed and been wrongly considered as idiopathic anaphylaxis [31]. Therefore, taking an extensive history is necessary, and anaphylactic reactions after up to six hours after ingestion of meat have to be taken into account. In patients ingesting kidney or other innards, the reaction may start earlier. The patients may be atopic, however, non-atopic individuals are also affected. Cofactors, such as effort and alcohol, may be contributing [16]. Not all patients react at every exposure; high sIgE titres and/or cofactors appear to be necessary. Also, African patients with sIgE to alpha-gal induced by parasitic infestations appear not to suffer from any allergic consequences [7].

The commercially available skin prick tests for meats and even with raw meats using the prick-to-prick method are not very sensitive. Skin prick and intradermal tests with cetuximab (5 µg/ml) [32] are an option and give better results [33], however, costs are high. Positive skin tests to cat may be due to the presence of IgE to cat IgA, although there is no associated clinical relevance to respiratory symptoms. Currently, there are commercial IgE assays available to measure sIgE to different mammalian meats (beef, pork, lamb, *etc.*) and alpha-gal (Thermo Fisher Scientific, Waltham, MA, USA). Also, sIgE to gelatins can be measured. A commercial assay for antidrug antibodies (ADA) to cetuximab does not exist, however, as mentioned, skin tests with cetuximab are reliable and sIgE to alpha-gal can be measured in such patients.

Histamine release tests or basophil activation tests can be performed with fresh meat or inner organs, *e.g.* pork kidney or with cetuximab [33]. They show, for example, positive test results based on expression of CD63 and CD203c on basophils (*figure 3*).

Food challenge with meat in alpha-gal-sensitized patients has again shown a long delay in the occurrence of symptoms [34]; with pork kidney, a shorter onset and severe reactions upon small quantities was observed [15]. In some patients, tryptase increased after around 3-5 hours, and in sequential basophil activation tests, the greatest expression of CD63 was present at around four hours [34]. This explains, in part, the long delay in the reactions and their severe nature upon exposure.

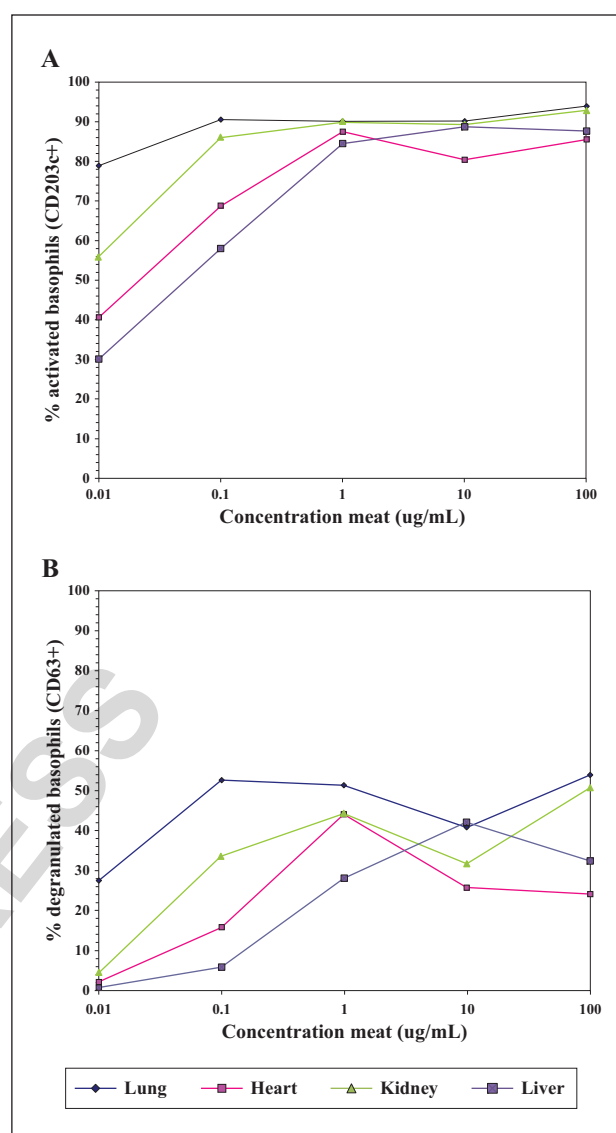


Figure 3. Basophil activation tests based on CD203c and CD63 expression using different innards from goat (Patient 2); (A) CD203c+ activated basophils; (B) CD63+ degranulated basophils. The patient had only eaten and reacted to goat's lung, the stimulation with other innards likely represents cross-reactivity to alpha-gal.

Case reports

We have previously reported four cases in which skin and basophil activations tests with cetuximab and raw pork kidney were a useful tool to identify sensitization [33]. Here, we briefly outline another four cases with some different aspects of the clinical manifestations and sensitization patterns (*table 1*). Two male patients had no atopic background but food allergy to red meat and innards only, particularly at night time. The manifestation of severe symptoms was dependent on cofactors for both, such as alcohol, although mild gastrointestinal symptoms were often present during the day time. In Patient 2, a very severe reaction occurred to goat's lung and alcohol. In the two young females,

Table 1. Summary of four patients with allergic manifestations from red meat and innards.

Patient Gender, age	Patient 1 Male, 53 years	Patient 2 Male, 62 years	Patient 3 Female, 20 years	Patient 4 Female, 31 years
Atopy symptoms Atopy screen (common pollens, moulds, mites, animal danders) Other hypersensitivity manifestations Other food allergy Allergic manifestation to alpha-gal and other foods	None Negative Anaphylaxis to pyrazolones Exanthem from amoxicillin None From the age of 22, occasional nausea, tachycardia and generalized urticaria, particularly at night. Previously, always eaten red meat in large quantities, associated with the consumption of alcohol. Red meat resulted in gastro-intestinal disturbance and diarrhoea	None Pollen, cat negative None None From the age of 51 approx. Twice a year: urticaria, dyspnoea and diarrhoea, vertigo, and vomiting. Occurred at night with a latency of 2-3 hours after meals. The most severe reaction involved goat lung with alcohol. At noon, small amounts of red meat and sausages were tolerated	Rhinconjunctivitis Pollen, cat positive Atopic dermatitis Milk, egg, poultry, nuts, fruits From the age of 5, nausea, emesis, and urticaria from dried meat. For 15 years adhered to a strictly vegetarian diet without meat, poultry or fish/seafood	None Negative Celiac disease Eosinophilic esophagitis Wheat, poultry From the age of 16, celiac disease, and later food allergy from wheat products, poultry and eggs. At the age of 26, urticaria and angioedema after eating minced meat associated with effort. For the last years adhered to a strictly vegetarian and gluten-free diet.
Skin prick tests with meats	Commercial meats: Equivocal to beef, pork, lamb Native meats and entrails: positive to beef, veal, pork, lamb, pork kidney, and goat lung; poultry: poultry: negative Cetuximab: positive Rituximab: negative	Commercial meats: negative Native meats and entrails: positive to beef, veal, pork, lamb, pork kidney, and goat lung; poultry: negative Cetuximab: positive Rituximab: negative	Commercial milk and meat series: positive to cow's milk, casein, alpha-lactalbumin, egg white. Fish and seafood series: negative. Native meats: not done Cetuximab: positive Rituximab: not done	Commercial meats: positive to beef and mutton, pork, and turkey ovomucoid. Native meats: not done Not done
Skin prick and intradermal tests with monoclonal antibodies Total IgE (kU/L) Specific IgE (kU/L)	67 kU/L SX-1: < 0.10 kU/L Pork: 0.41 kU/L Beef: 0.84 kU/L Lamb: < 0.35 kU/L Horse: 0.27 kU/L Chicken: < 0.10 kU/L Seafood: < 0.10 kU/L Gelatine: < 0.35 kU /Cross-reactive carbohydrate determinants (CCD): < 0.35 kU /Bromelin (CCD from pineapple): < 0.35 kU/L	550 kU/L Pork: 4.00 kU/L Beef: 4.84 kU/L Lamb: 1.17 kU/L Chicken: < 0.10 kU/L Seafood: 0.38 kU/L	1000 kU/L Milk: > 100 kU/L Alpha-Lactalbumin (nBos d 4): 35.10 kU/L Beta-Lactoglobulin (nBos d 5): 37.00 kU/L Casein (nBos d 8): > 100 kU/L (class 6) Egg white: 14.70 kU/L () Egg yolk: 1.74 kU/L Ovalbumin (nGal d 2): 2.60 kU/L Ovomucoid (nGal d 1): 9.80 kU/L Chicken: 9.03 kU/L Nutmixture: 13.80 kU/L Seafood mixture: < 0.35 kU/L 4.70 kU/L	514 kU/L Beef: 11.1 kU/L Mutton: 9.10 kU/L Oat flour: 6.20 kU/L Gluten: 82.50 kU/L Turkey: 1.37 kU/L Cod: 2.87 kU/L rGad e 1 (main allergen cod): < 0.35 kU/L ImmunoCAP ISAC: rTri a 19:0101 (omega-5 gliadin): 2.4 ISU nTri a aA-TI (alpha-amylase / trypsin inhibitor): 2.1 ISU (ISAC standard units) 1.26 kU/L Not done
sIgE alpha-gal (kU/L) Basophil activation tests (CD 203c, CD63 expression)	5.8 kU/L Cetuximab: positive Rituximab: negative Activation and degranulation after stimulation with fresh pork kidney	71.0 kU/L Cetuximab: positive Rituximab: negative Activation and degranulation after stimulation with goat innards	Cetuximab: positive Rituximab: not done Activation and degranulation after stimulation with fresh pork kidney.	Not done

longstanding atopic disorders (Patient 3) or celiac disease and eosinophilic esophagitis (Patient 4), as well as food allergy to miscellaneous foods, including poultry, were present. Because of additional symptoms to red meat, both adhered to a strictly vegetarian diet. Only Patient 2 reported a severe and longstanding local reaction to a tick bite (*Ixodes sp.*), the other three patients had their symptoms already at young age, suggesting that other ways of sensitization may also be relevant.

Diagnosis was made based on history and confirmed by skin tests (the best results were to raw pork kidney, as previously suggested, or other innards), as well as measurement of sIgE to alpha-gal, and skin and basophil activation tests using cetuximab and innards.

Summary

It is now well known that allergic reactions to red meat exist and that they are mostly dependent on specific IgE to the carbohydrate alpha-gal, and rarely to other allergens. The sensitization most likely occurs by induction of IgE through tick bites, particularly to *Amblyomma americanum* in the U.S., but also to *Ixodes* species in other continents, such as Australia, Europe, Central America, and Asia. Clinical diagnosis may be delayed because of the atypical, delayed manifestation of the clinical symptomatology and, on the other hand, by the lack of sensitivity of skin tests with meats. Skin tests, with e.g. raw pork kidney, are more sensitive. The measurement of specific IgE to alpha-gal, skin tests, and basophil activation tests, with e.g. cetuximab, are more reliable. A particular clinical feature is the late onset of anaphylaxis and often the requirement of cofactors, such as exercise, alcohol, and others, to elicit the reaction. Other allergenic sources, such as gelatins, are currently rare, but have to be taken into account in exposed patients. ■

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