

Review

Mammalian meat allergy

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Abstract

Mammalian meat allergy is an allergic reaction mediated by IgE antibodies directed against the mammalian oligosaccharide epitope galactose- α -1,3-galactose. Clinically, it is characterized by a range of symptoms including urticaria, angioedema, gastroenteritis, and anaphylaxis hours following ingestion of red meat. It is an emergent allergy in tick endemic areas across the world. As a recently described disease with a cutaneous presentation, dermatologists should be familiar with this entity and recognize it as a differential diagnosis for urticarial and anaphylaxis reactions.

Introduction

Mammalian meat allergy is a recently described disease with a characteristic clinical presentation. Patients without any prior history of allergy become sensitized to the mammalian oligosaccharide epitope galactose- α -1,3-galactose (α -gal) following a tick bite. Thereafter, IgE antibodies develop, and upon consumption of red meat products, patients develop a range of delayed symptoms including urticaria, angioedema, gastroenteritis, and anaphylaxis. It is known to affect both adults and children and was first reported in 2007 by van Nunen *et al.*¹ after encountering 25 cases of this phenomenon in Sydney, Australia. As well as a delayed allergic reaction to the consumption of red meat, these individuals also have an immediate onset anaphylactic reaction upon exposure to the epidermal growth factor receptor (EGFR) inhibitor cetuximab.² As tick bites are common in many regions of the world,³ it is pertinent for dermatologists to gain familiarity with this emergent allergy as a potential cause for idiopathic delayed urticarial and anaphylaxis reactions.

Pathophysiology

The carbohydrate galactose- α -1,3-galactose is a complex oligosaccharide moiety constituted from two galactose molecules by the enzyme alpha-galactosyl-transferase.⁴ It is present on many different types of proteins and thus prone to cross-reactivity.⁵ Notably, it is a blood group substance found in glycolipids and glycoproteins of nonprimate mammals. It is also found on the Fab portion of the chimeric mouse-human monoclonal antibody cetuximab.⁶ It has been shown through

inhibition studies⁷ and staining⁸ that α -gal is carried on ticks, and it is well-established that initial sensitization to α -gal occurs through tick bites. However, it is unclear why tick bites are able to produce such high levels of IgE and why these antibodies are directed so specifically at α -gal and not other oligosaccharides found in the tick.⁹ It is understood that for IgE to be produced specific to α -gal, a provoking agent (tick bite) is needed to generate a state of allergy proneness promoting the development of a Th2 cytokine profile whereby class-switching to IgE can occur. These IgE antibodies will be specific for either α -gal, tick salivary proteins, or both; however, the tendency toward developing the α -gal allergy is dependent on individual susceptibility.^{4,10}

Tick bite

Ticks are ectoparasites found in many temperate and tropical zones around the world. These parasites spread a greater array of pathogens than any other arthropod vector group.¹¹ Almost all ticks belong to two major subgroups: hard-bodied ticks (*Ixodidae* species) or soft-bodied ticks (*Argasidae* species).¹² The tick is an important vector for many diseases, including Lyme disease caused by *Borrelia burgdorferi*,¹³ Rickettsial infections, Colorado tick fever, relapsing fever as well as toxin-related illnesses such as tick paralysis.¹⁴ Clinical presentations can vary from local allergic reaction to severe anaphylaxis. In America, *Amblyomma americanum* has been implicated in α -gal sensitization as well as *Ixodes holocyclus*, in Australia; however, other species of ticks have also been suspected to cause sensitization internationally (Table 1).¹⁵

Table 1 Tick species suspected to cause mammalian meat allergy globally

Region	Suspected tick species
United States	<i>Amblyomma americanum</i> ⁸
Panama	<i>Amblyomma cajennense</i> ¹⁷
Brazil	<i>Amblyomma sculptum</i> (<i>cajennense</i> complex) ³¹
Australia	<i>Ixodes holocyclus</i> ⁴
Europe (France, Germany, Spain, Sweden, Switzerland, Norway, Italy)	<i>Ixodes ricinus</i> ^{8,18,27,28,32–35}
Japan	<i>Haemaphysalis longicornis</i> ³⁶

Delayed anaphylaxis: mammalian meat allergy

Traditionally, anaphylaxis has been recognized as a syndrome that occurs rapidly after exposure to allergens causing constellations of angioedema, urticaria, hypotension, respiratory symptoms, and cardiovascular collapse. As the characteristic delay in symptoms for patients with this allergy does not fit with traditional definitions, its discovery has piqued research into the causation of this delay. The dominant hypothesis presently is that as a cross-reactive carbohydrate, α -gal must be processed by the digestive system before slowly entering the circulation in its allergenic form.¹⁶ α -gal is abundantly present on the surface of both glycolipids and glycoproteins of several mammalian meats⁸ as reported in Table 2. It is hypothesized that the delay in symptoms of several hours correlates with the transit time required for lipid absorption and chylomicron packaging.¹⁷ It is only after this process that chylomicrons like very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) are able to slowly enter the bloodstream. Consequently, the presence of α -gal on the surface of VLDL and LDL initiates a cross-linking of IgE thus stimulating mast cell mediator release and the potentiation of an anaphylactic allergic reaction.⁹ Still, the question remains as to which specific glycolipid or glycoprotein is the carrier of α -gal and thus the catalyst for this allergic reaction.¹⁷ More recent work has shown that cofactors like exercise or alcohol can increase intestinal absorption and thus decrease the timeframe between ingestion and onset of allergic symptoms.¹⁸

Table 2 Precipitants of mammalian meat allergy

Immediate reactions	Delayed reactions
Cetuximab	Beef, pork, lamb, squirrel, rabbit, horse, goat, venison, kangaroo, seal, whale Gelatin (less commonly) Dairy products (less commonly)

Immediate anaphylaxis: cetuximab

Cetuximab is a recombinant human-mouse chimeric EGFR monoclonal antibody used in the treatment of squamous cell carcinoma of the head and neck and in metastatic bowel cancer.^{19,20} During its clinical trials in 2007, O'Neil *et al.*²¹ reported an increased incidence (22%) of grade 3 or 4 hypersensitivity reactions during or after first infusion in certain American states as compared to the international average of $\leq 3\%$. These same patients also reported having episodes of delayed anaphylaxis after ingesting mammalian meat.⁶ Analysis of the affected patients' serum revealed pre-existing IgE antibodies to an oligosaccharide present on the monoclonal antibody which was later identified by Chung *et al.*⁶ as α -gal. Through analysis of cetuximab-specific IgE antibodies, α -gal residues have been found on both Fab segments of the monoclonal antibody allowing for an efficient cross-linking of IgE on mast cells.⁶ Its progression is distinct from symptoms of mammalian meat allergy as reactions are rapid and often peak within 20 minutes of intravenous administration, occasionally proving to be fatal.²¹ In patients with mammalian meat allergy and chemotherapy-refractory metastatic malignancy, the EGFR inhibitor panitumumab, a human antibody, has been reported as an alternate therapeutic agent.²² Similar acute immunological responses have been observed in patients with mammalian meat allergy exposed to infliximab and snake antivenom in isolated case reports.^{23,24} Notably, all these cases of acute reactions to α -gal have occurred when the culprit allergen has been introduced intravenously.

Clinical features

Clinicians should consider mammalian meat allergy as a differential diagnosis in patients presenting with recurrent episodes of generalized urticaria, angioedema, gastroenteritis, or anaphylaxis with no immediate cause. Adults and children can both present with severe allergic reactions without an immediate precipitant. Upon further questioning, patients may produce a positive history of a large local reaction to a tick bite; however, this is not always the case.¹⁵ Increased suspicion should be placed on patients who report spending a large amount of time outdoors or individuals living in tick-endemic areas.^{25,26} Frequently reported symptoms include nausea, diarrhea, indigestion, urticaria, and angioedema usually preceded by generalized pruritus often occurring in the middle of the night.² Upon interrogation, patients disclose consumption of some form of mammalian protein 3–6 hours before onset of symptoms.²⁵ In addition, patients describe longstanding tolerance to red meat years before onset of symptoms⁷ and continue to tolerate poultry and fish.²

Investigation

Initially many patients tested with conventional skin prick testing (SPT) using commercial extracts of mammalian meat (beef,

pork, lamb) produced negative results (small wheals 2–4 mm diameter).^{2,4,17,25} As these SPT reactions do not produce robustly positive results, a diagnosis of mammalian meat allergy may be discounted which could lead to incorrect management and potentially serious anaphylaxis. SPT with freshly prepared meat extract will elicit a strongly positive result in affected patients, and accordingly this appears to be the best means of testing for mammalian meat allergy.^{2,17,25} Accumulating evidence suggests that SPTs using cetuximab can be used to assist diagnosis, skin reactivity is often impressive and rapid, and thus this reagent could potentially be incorporated into clinical practice.^{27–29} Although oral food challenge remains the gold standard in the diagnosis of food allergies, it is currently not recommended for mammalian meat allergy due to the 3–6 hour delayed timeframe and the likelihood of anaphylaxis.² Serological testing may be conducted specifically looking for α -gal specific IgE and mammalian meat specific IgE, which should be consistently elevated.³⁰

Management

As many patients note, severity and timing of symptoms are highly variable with every exposure to red meat, thus it is important to educate the patient that they have an “anytime risk, but not an every time risk” of anaphylaxis.⁴ The mainstay of management involves carrying an epinephrine auto-injector and if anaphylaxis does occur, prompt treatment with antihistamines, epinephrine, steroids, and intravenous fluid resuscitation.⁹ Physicians also need to properly inform patients of their risk of immediate onset anaphylaxis when taking cetuximab. Prevention of future allergic reaction relies on the avoidance of all mammalian meat and mammalian meat derived products in those who develop allergic reactions to gelatin and dairy products.² Dietitian input is invaluable in this setting for counseling about avoidance of mammalian meat products and consideration of the need for supplementation of iron and Vitamin B12, particularly for those who are sensitized to gelatin and mammalian milk.⁴ As there is currently no cure, to prevent α -gal sensitization, it is important to avoid and reduce the risk of tick bites by wearing protective clothing and carefully checking for ticks when undressing. Wearing lighter colored clothes makes ticks more visible, which may be of benefit to those living in a tick-endemic area. The use of DEET-containing insect repellent or permethrin-treated clothing is also highly recommended.^{9,31}

Conclusion

Mammalian meat allergy is a new diagnosed syndrome with a unique pathophysiology and constellation of clinical syndromes. For patients with unexplained causes of recurrent urticaria, angioedema, or anaphylaxis with a history of tick exposure, it should be considered as a differential diagnosis.

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