Guest Review

‘MIDNIGHT ANAPHYLAXIS’ TO RED MEAT IN PATIENTS WITH ALPHA-GAL SENSITISATION: A RECENT DISCOVERY IN THE FOOD ALLERGY WORLD AND A CASE REPORT FROM SOUTH AFRICA

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INTRODUCTION

A syndrome of delayed anaphylaxis to red meat, occurring in geographical ‘clusters’ initially identified in the United States, was first described in 2009. A few years later, this enigmatic anaphylactic reaction was ascribed to IgE antibodies to galactose-alpha-1,3-galactose (alpha-gal), an oligosaccharide, which is a major blood group substance in non-primate mammals. It appears that the predominant source of sensitisation to alpha-gal is bites from certain ticks.1–4 Since 2009, several hundreds to thousands of cases of delayed red-meat allergy have been described worldwide, but very few reports have come out of Africa. This case series describes 2 cases of an acquired form of delayed anaphylaxis to beef and mutton in patients who were subsequently found to be highly sensitised to alpha-gal, residing in the same region.

CASE 1

Mr HS is a 63-year-old male from George, South Africa, who is generally fit and well, apart from psoriasis, for which he is on topical treatment. He grew up on a cattle farm and has in the past spent a significant amount of time in the ‘veld’ (open country). He also currently resides on a golf estate adjacent to a cattle farm. He has no past history of food allergy apart from an episode suggestive of MSG-syndrome after a Chinese meal 15 years ago. Around one year ago HS ate out for dinner and, unexpectedly, experienced an urticarial rash three hours after the dinner with, at that stage, no clear trigger. The rash occurred mainly at active psoriasis sites. Subsequently, similar symptoms started occurring repeatedly, especially after he had eaten out, always about three hours later. On a different occasion after eating steak and chips, he experienced a severe attack with diffuse urticaria and tightening of the throat three hours after eating, for which he was hospitalised and given intravenous antihistamines (please note that intramuscular adrenaline would have been preferable to antihistamines for these symptoms). Over the course of this past year, he has experienced about ten episodes of an allergic reaction, always three or more hours after eating, two of which required hospitalisation for severe symptoms.

After a few episodes, HS started recognising that he had always eaten red meat before such symptoms occurred. The main cause was beef; lamb caused milder symptoms, which could usually be minimised by taking an antihistamine before eating the lamb.

HS discussed the symptoms with his family practitioner, and after discussion with an allergist the diagnosis of delayed-type allergy to red meat as a result of alpha-gal sensitisation (so called ‘midnight anaphylaxis’, as symptoms often occur several hours after the evening meal) was entertained. Blood tests showed results as follows:

- Specific IgE to beef: 1.26 kU/l
- Specific IgE to mutton: 0.34 kU/l
- Specific IgE to alpha-gal: 29.6 kU/l.

The diagnosis of alpha-gal allergy was confirmed, and HS was advised to avoid meat of mammalian origin, especially beef, which caused more severe symptoms in his case. He was also given an emergency treatment plan in case of reactions.

CASE 2

Shortly after diagnosing HS with alpha-gal syndrome, another similar case in the same region became apparent. CD is a 71-year-old male who happens to reside in the same golfing estate as HS – adjacent to the same cattle farm. About three years ago CD first started experiencing
unexplained urticarial rashes in the late evenings and early hours of the morning. He had no respiratory symptoms. He recalls being bitten by a tick four years ago. For a long time he could not link specific foods to the development of the rashes, despite many visits to doctors, numerous allergy tests and using topical and systemic corticosteroids to try and control the symptoms. For years he pursued a varied exclusion diet to no avail. CD’s sister-in-law, a nursing sister from England, then suggested a possible link to meat allergy and, on the advice of a local laboratory, she arranged an IgE test for alpha-gal which came back positive at 19.3 kU/l. Once this link had been established, CD realised that he reacted consistently to red meat (lamb more so than beef; minimally to pork) approximately six hours after ingestion. Elimination of lamb and beef was advised, and a fast-acting antihistamine such as cetirizine was prescribed in case accidental red-meat ingestion led to urticaria.

**DISCUSSION**

Relatively recent research in the past decade has identified a novel IgE-mediated antibody response which can lead to two distinct forms of anaphylactic reaction: the first is a delayed onset reaction after the ingestion of food products of mammalian origin. The second is immediate-onset anaphylaxis during the first exposure to the intravenous chemotherapeutic agent, cetuximab. In both cases, tick bites are the significant cause of the initial IgE-response. These reactions can occur at all ages and do not appear to have a predilection for otherwise atopic individuals.

**ALPHA-GAL SENSITISATION AND REACTIONS TO RED MEAT**

The syndrome of ‘midnight anaphylaxis’ to red meat describes a delayed-onset allergic reaction three to six hours after eating mammalian food products. Patients typically react to beef, mutton or pork, but have no trouble with chicken or fish. The responsible IgE antibody for this type of reaction is not to a major protein allergen specific to the meat; rather it is to the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal). Alpha-gal is found in all mammalian cells, but not in the tissues of humans and Old World monkeys. The kidneys appear to be particularly rich in alpha-gal.

Most reports of delayed meat allergy due to alpha-gal cross-reactivity have been described in adults, who classically present with an acute onset of delayed anaphylaxis and urticaria. However, a few recent cases have been described in the paediatric population. Unlike their adult counterparts, it appears that the majority of children with alpha-gal syndrome present with urticaria rather than anaphylaxis.

Sensitisation to alpha-gal may occur through tick bites, possibly via parasitic infection or through exposure to cetuximab, a chimeric IgG1 monoclonal antibody against the epidermal growth factor receptor, used in treating colon and squamous carcinomas. Skin-prick tests with commercial extracts to meat are often equivocal, and specific antibodies to red meat extracts often show low positive results only despite a severe reaction, as seen in this case. Specific IgE to alpha-gal, however, is clearly positive in this type of allergy. Moreover, patients with this syndrome also classically test positive to cat on SPT and specific IgE, as cat IgA has an alpha-gal epitope. However, IgE to alpha-gal does not create a risk for asthma.

Bites from certain types of ticks have been described as the initial causes of sensitisation to alpha-gal (see Figure 1). Ticks (Ixodida) are obligate bloodsucking parasites, an order within the class Arachnida. Several ticks are known to feed on non-primate mammals as their primary host. In the United States, bites from the lone star tick *Amblyomma americanum* are causative (see Figure 2); this was established by correlating the IgE antibodies to alpha-gal, the IgE antibodies to this tick and from the known distribution of this tick. In Australia, *Ixodes holocyclus* and in France *Ixodes ricinus* appear to be responsible. Studies in Sweden have reported clear evidence that the alpha-gal epitope is present in the gut of the tick *Ixodes ricinus* and can be transmitted via saliva during a tick bite.

In Africa, alpha-gal-positivity has been described in Harare with possible causative candidates including helminths, scabies and ticks; however, associated cases of delayed reaction to meat have seemingly not been published previously in Africa. It is interesting that the two cases from South Africa described above lived in the same golfing estate and adjacent to a cattle farm. This raises the possibility that a particular local tick species was responsible for the initial sensitisation. Since discussing these case reports, other South African allergologists have described further unpublished cases in Cape Town (personal communication, Paul Potter) and possible (strong history but not confirmed by blood tests) cases in the rural Eastern Cape (personal communication, Michael Levin).
Patients with anaphylaxis to red meat due to alpha-gal sensitisation typically present three to six hours after ingestion, which is a far longer interval than classical IgE-mediated reactions. Because of this delay in symptoms, the allergy often goes undiagnosed for some time or is ascribed to idiopathic anaphylaxis before the pattern is recognised. Other nuances of this type of reaction are that dose, temporal relation to tick bites and fatty content of the meat appear to influence the allergic reaction.\(^2,3\) Frequently, a small amount of mammalian meat is tolerated, but larger amounts lead to a reaction; the more meat that is consumed, the more severe the reaction tends to be. Reactions to red meat and even dairy are more easily elicited if the patient has recently had a tick bite (in the preceding one to four weeks). The IgE to alpha-gal can decrease over time but the trend can be reversed by recent tick bites. It also seems that fattier meats provoke episodes more consistently and more severely.

The reason for the characteristic delay in the presentation is poorly understood. Given the fact that the lipid content of the meat influences the reaction, it may be that lipid absorption is a rate-limiting step in the delay.\(^3\) Chylomicrons, which are large fat-containing particles, enter the bloodstream three to four hours after a meal. This is a possible explanation for the delay of three hours before symptoms tend to occur.

The delayed anaphylaxis syndrome to mammalian meat caused by alpha-gal sensitisation differs from the ‘pork-cat syndrome’, in which patients develop an IgE to cat serum albumin (Fel d 2) that cross-reacts with porcine albumin. In the pork-cat syndrome patients can develop a severe allergic reaction on consuming pork, but usually within 45 minutes to an hour after consumption.\(^11,12\)

**ALPHA-GAL SENSITISATION AND ANAPHYLAXIS TO CETUXIMAB**

The concept of the antibody to alpha-gal came to light because of a regional clustering of reactions to cetuximab in the United States.\(^13\) Cetuximab is a monoclonal antibody produced in a mouse cell line. Unlike the cross-reactivity syndrome with mammalian meats, the reaction to cetuximab tends to be immediate and often on first exposure. Such hypersensitivity reactions were reported in up to 20 per cent of people using cetuximab in Tennessee or North Carolina,\(^13\) and research has shown that the reactions were caused by pre-existing antibodies to the alpha-gal oligosaccharide on the Fab portion of cetuximab.\(^14\) The distribution of the pre-existing antibodies was noted to correlate with areas with the highest prevalence of Rocky Mountain Spotted Fever, which led to more detailed research into tick bites as an associated factor. A rise in IgE to alpha-gal was demonstrated after tick bites,\(^8\) which led to the finding that tick bites were the original source of sensitisation to alpha-gal.

**ALPHA-GAL SENSITISATION AND REACTIONS TO MILK**

Apart from being found in meat, alpha-gal is also found in mammalian milk, including cow’s milk and goat’s milk.\(^3\) It is possible to have an allergy to the alpha-gal component of milk rather than the classical protein component. This entity should be considered in late-onset milk allergy in subjects over the age of five years as an alternative to cow’s milk protein allergy. However, this has, to date, been poorly described and the prevalence of this type of milk allergy is unknown.

**CONCLUSION**

Allergy to mammalian meat secondary to alpha-gal sensitisation is a newly understood food allergy with increasing case reports worldwide. Although there is evidence of alpha-gal sensitisation in Africa, previous reports of meat allergy have been rare there. This case report demonstrates typical features of ‘midnight anaphylaxis’ with strongly positive allergy tests to alpha-gal. Increased awareness of the characteristic features of this type of allergy will lead to more astute diagnosis and more precise management of cases that may previously have been ascribed to idiopathic anaphylaxis.

**REFERENCES**

1. Michel S, Scherer K, Heijnen IA, Bircher AJ. Skin prick test and basophil reactivity to cetuximab in patients with IgE to alpha-gal and allergy to red meat. Allergy 2014;69:403–405.