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Speculations on red meat allergy due to α-Gal; its connection to coronary artery disease, suggested dietary guidance and allergy testing

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To the Editor,

in 2009, we reported a case-report of generalized allergic reaction during the performance of allergy tests to red meats (1). It was the case of a 59-year-old male, with a 10-year-long anamnesis of several anaphylactic episodes (urticaria-angioedema and asthma attacks) 2 hours after the consumption of mammalian meats. He was tolerating dairies and avian meat. His medical history was including seborrheic dermatitis, gastric ulcer, coronary artery disease (CAD) and symptoms of exercise-induced bronchospasm (1). Since all reactions were reported to happen after the ingestion of well-cooked meat we concluded that the culprit allergen was heat-stabile, without being able to specify it. Two more cases of allergy to red meat, males, 68-year-old and 52-year-old respectively, were referred to us last year, both confirmed with skin prick tests. The 68-year-old patient reported tolerating small quantities of cold cuts. They both had anamnesis of CAD; the 68-year-old patient had a stent placement (14 years ago), while the 52-year-old patient was under conservative medical treatment (for the last 6 years). At that time, CAD had been recently described as comorbidity to mammalian meat allergy and α-Gal allergen was inculpated (2). Patients' sensitization to α-Gal was later confirmed with specific IgE test (sIgE) against this allergen. We tried to contact the first case of meat allergy in order to prescribe the same test, but unfortunately we were informed that he had passed away due to myocardial infarction.

In the 2010s, tick bites were recognized as the main "sensitizer" to α-Gal, causing cross-allergic reactions to mammalian meat (3). Our patients are located in the rural area of the island of Euboea, Greece, engaged in outdoor activities and tick bites seem the most reasonable explanation of their sensitization. They confirmed anamnesis of tick bites but couldn't define the time. Three genera of *Ixodidae* family are the main ticks parasitizing humans in Greece; *Rhipicephalus*, *Ixodes* and *Hyalomma* (4). Al-

though not all tick bites cause IgE-sensitization to α-Gal, the above mentioned do (3, 5).

Alpha-Gal has been recognized as the culprit allergen for severe and fatal anaphylaxis to the mAb cetuximab, while case-reports have been published also for drugs like heparin, vaccines and anti-venom (3, 6). Although parenteral administration can cause immediate allergy, food allergy due to α-Gal is commonly expressed with a delay in symptom onset and is dose-unrelated; features also noticed in our cases (7-9). The pathophysiological mechanism differs when α-Gal is administered *via* the parenteral route than intake *via* the gastrointestinal system. α-Gal parenteral administration (*e.g.*, injection of cetuximab) triggers an acute IgE-mediated reaction, while a delayed allergy is observed when it enters through the digestive system.

The pathophysiological background of the "digestive" delay has been elucidated by an *in vitro* study, analyzing the transport of α-Gal through the intestinal epithelium (10). It was found that only the lipid-bound α-Gal is able to cross the intestinal epithelium, while protein-bound α-Gal was not detected in the basolateral media of enterocytes (10). Alpha-Gal contained in glycolipids is digested, absorbed, and enters the blood stream by the thoracic duct about 2 hours later, explaining the late-onset of allergic symptoms (3, 10). Furthermore, in α-Gal allergic patients, dairies may cause delayed onset of gastrointestinal symptoms over 2 hours (11).

There is a strong epidemiological connection between CAD and "α-Gal syndrome", a term used to describe different clinical allergies due to this allergen (12). This relationship has been confirmed by a study using intravascular ultrasound imaging in subjects undergoing cardiac catheterization (2). A mechanistic model has been proposed to clarify this connection, describing the delivery of α-Gal epitopes - connected to lipid particles - to mast cells within atherosclerotic plaques (12).

Due to the intraindividual tolerability to the culprit allergen, patients with α-Gal allergy exclude or reduce mammalian meat from their diet, but often consume tolerable quantities of products containing α-Gal. This can induce local mast cell degranulation leading to chronic mast cell activation and pro-inflammatory events contributing to the chronic inflammatory procedures of CAD pathogenesis (12). Our objection to this theory is that if mast cells play a pivotal role to this inflammation, red meat ingestion would cause a massive mast cell degranulation in atherosclerotic plaques so angina would be a common symptom of the deayed-type allergic reactions to red meat, resembling to Kounis Syndrome (13).

The hypothesis that small tolerable quantities cause the ongoing coronary inflammation *via* local mast cell degranulation is an emerging concern for us. Based on the knowledge that participation of chylomicrons and inflammation are common parameters of CAD and α-Gal sensitization, their exact immunological connection remains to be clarified. In order to avoid worsening of CAD by accumulation of lipoproteins containing α-Gal, we recommend the strict avoidance of all α-gal containing food, regardless the tolerance-level of each patient; dairies, gelatin and mammalian meat products should be avoided. Further large scale studies including metabolomic changes in such patients, can induce more clear evidence and conclusions.

Six prick-to-prick tests (fresh food) along to 3 SPT (HAL Allergy, The Netherlands) to red meats (beef, pork, mutton) had been used in our first case, leading to an unpredictable quantity of "fresh" allergen that penetrated skin, causing anaphylaxis. Prick-to-prick tests to a variety of fresh allergens of the same food group are performed in order to detect/exclude any differences in sensitization. In the case of mammalian meat products α-Gal appears to be present in all of them, but its concentration is higher in innards than in muscle meat (14).

Regarding the diagnostic procedures for red meat allergy, skin tests can set the diagnosis of allergy to red meat, but their low concentration of α-Gal may result in low sensitivity, as formerly reported (15, 16). On the contrary a blood assay for sIgE to α-Gal is more sensitive to confirm or set the diagnosis of α-Gal syndrome.

Skin tests with the use of commercially available SPT extracts were positive in all our cases. The precept from our initial case was that initially SPT with commercial extracts should be used and in the case they result positive, prick-to-prick should be omitted, in order to avoid the extremely rare - but possible - case of a systemic reaction. The use of prick-to-prick to different meat products are suggested as the next step to SPT, since they can offer additional information in cases of equivocal SPT (15, 16). Oral food challenge is considered the diagnostic gold standard for dubious cases, however in the case of red meat allergy the particularly delayed and potentially severe expected reactions suggest that this procedure can be carried out only to monitored inpatients.

Concluding, until larger epidemiologic, clinical and lab studies will clear the landscape of the connection between CAD, atopy and mammalian meat allergy (**table I**), it would be wise to advice and educate patients with α-Gal allergy for a strict avoidance of all α-Gal containing products and prescribe a regular cardiovascular check-up. The other way around, CAD patients should be probably checked for α-Gal sensitization in order to avoid accumulated inflammatory complications.

Conflict of interests

The authors declare that they have no conflict of interests.

Table I *- Unmet needs for α-Gal and the related CAD pathogenesis.*

Is the use of α-Gal-containing medications also connected to an increased risk of CAD?
What is the real impact of α-Gal ingested as food traces, on the pathogenesis of CAD in allergen-sensitized subjects with no red meat allergy?
Should the diet of a person sensitized to α-Gal be completely α-Gal-allergen-free?
If "lipid-bound α-Gal" is causing the chronic inflammation underlying CAD pathogenesis, is there the possibility that another food might also connect with CAD?
Should an α-Gal sIgE lab test be prescribed to all CAD patients?
Should α-Gal be mentioned in food labeling?
Is it possible to produce a commercial SPT extract of α-Gal? Can it be produced by red meat or ticks?

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