Speculations on the connection of α-Gal allergy to Coronary Artery Disease.

Constantinos Pitsios[1], Anastasia Dimitriou[2], and Emilia Vassilopoulou[3]

[1]University of Cyprus
[2]Allergy Private Practice Network
[3]International Hellenic University

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Σπεςυλατιονς ον τηε ςοννεςτιον οφ α-Γαλ αλλεργψ το ὃροναρψ Αρτερψ Δισεασε.

Pitsios Constantinos[1,2], Dimitriou Anastasia[2], Vassilopoulou Emilia[3].

1. Medical School, University of Cyprus, Nicosia, Cyprus

2. Allergy Private Practice Network, Athens, Greece

3. International Hellenic University, Department of Nutritional Sciences and Dietetics, Thessaloniki, Greece

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Corresponding author :

Constantinos Pitsios

Medical School, University of Cyprus

Panepistimiou 1, 2109 Aglantzia

Nicosia, Cyprus

Tel; +30 6974348638

Email; pitsios.constantinos@ucy.ac.cy

Statement:

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Pitsios C, was the main author and clinical supervisor.

Dimitriou A; drdimiana@gmail.com , was the clinician of the cases reported and reviewed the paper.

Vassilopoulou E; vassilopoulouemilia@gmail.com , has contributed as author to the diet suggestions and as reviewer.

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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 meat products [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 (yo) and 52yo respectively, were referred to us last year, both confirmed with skin prick tests. The 68yo patient reported tolerating small quantities of cold cuts. They both had anamnesis of CAD. 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. Three genera of *Ixodidae*Family are the main ticks parasitizing humans in Greece;*Rhipicephalus* , *Ixodes* and *Hyalomma* [4]. Although 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]. 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 [6]. The pathophysiological mechanism differs when α-Gal is administered*via* the parenteral route than intake *via* the gastrointestinal system. α-Gal parenteral administration (i.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 [7]. 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 [7]. Alpha-Gal contained in glycolipids is digested, absorbed and enters the blood stream by the thoracic duct after hours, explaining the late-onset of allergic symptoms [3, 7]. Furthermore in α-Gal allergic patients, dairies may cause delayed onset of gastrointestinal symptoms over 2 hours [8].

There is a strong epidemiological connection between CAD and "α-Gal syndrome", a term used to describe different clinical allergies due to this allergen [9]. 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 [9].

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 [9]. Our objection 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 delayed-type allergic reactions to red meat, resembling to Kounis Syndrome.

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. Can α-Gal molecules generate the inflammation, as plaque's component, maybe through a process of immune-complexes? Are they inducing transdifferentiation of vascular smooth muscle cells to macrophages or local proliferation of monocytes and formation of foam cells?

Immunological pathophysiology of CAD is still unclear, while on the other hand epidemiological data seem definite and alarming. 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. Thus, dairies, gelatin and mammalian meat products should be avoided.

Should a patient with CAD be tested for α-Gal? Screening *in vivo*and *in vitro* tests have been established as prevention in the field of Cardiology. The impact of α-Gal should further be investigated and compared between areas with high prevalence of sensitization due to tick bites and tick bites free. Metabolomic profiling of such patients will clarify the future of α-Gal allergy.

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