



Case Report

A Case Report on Alpha-gal Syndrome

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Abstract

The alpha-Gal syndrome (AGS) is a relatively newly recognized food allergy in which patients develop sensitization to meat after being bitten by specific tick species. AGS causes a delayed IgE mediated allergic reaction after consumption of meat and sometimes-dairy products and currently it is treated by avoiding consumption of allergens. Here we present a patient who has been living with AGS for about 20 years.

Keywords: Alpha-gal; Mammalian meat allergy; Tick borne illness

Introduction

Several features of the alpha-Gal syndrome (AGS) make it a complex and unique form of food allergy. Patients with a-Gal syndrome are primarily sensitized to meat and sometimes dairy product via a tick bite. This syndrome causes a delayed allergic reaction, ranging from hives and rash to anaphylaxis, initiated by IgE antibodies against carbohydrate galactose-a-1,3-galactose (a-Gal). Currently skin prick test using commercial extracts of meat is not good diagnostic test and as there are no curative treatment for AGS and patients are advised to avoid allergens.

Case Presentation

A 52 year old female presented to her primary care with a tick attached to her belly and a surrounding rash. She was experiencing fever up to 101, chills, myalgia and unsure how long the tick had been attached. Her vitals were stable. The rash was a classic bull's eye rash that is with a red center surrounded by a clear ring, non-

itchy, slightly tender to palpation with slightly raised borders. Rest of the exam including cardio-pulmonary, abdominal, neurological were within normal limits. The tick was removed in the clinic and patient was sent home with a 14-day course of oral doxycycline. Labs for Lyme disease as well as tick borne panel were sent which came back positive for IgM antibodies for Lyme disease. 2 weeks later patient was followed at the clinic when it was found that her overall symptoms did improve somewhat but she continued to have myalgias, severe fatigue and generalized weakness due to which the doxycycline course was extended to 28 days total. Around 8 weeks after, patient was almost back to her baseline when she was out for a picnic and consumed pork, soon after which she developed raised itchy rash on her face and body with swelling around her lips and some difficulty breathing. She knew she was experiencing an allergic reaction and was unsure why it had happened as she had experienced no issues with consuming pork before. She took some diphenhydramine which helped her symptoms but did not seek medical attention. 2 weeks later a similar episode of rash and lip swelling occurred when she consumed chicken, which was a regular on her diet prior. This time too she took diphenhydramine which helped her symptoms.

Patient, by occupation was a researcher and her husband an epidemiologist who researched about patient’s ongoing symptoms themselves and came across “alpha-gal syndrome” which they found was a new onset allergic reaction that can occur to eating mammalian meat. They also found that this syndrome could many a times develop after being bitten by a certain type of tick. Given the recent history of tick bite in patient and then the development of new onset allergy to eating mammalian meat, patient was quite concerned about her developing alpha-gal syndrome. At this point, patient saw an allergist who then conducted a blood test to look for antibodies for alpha-gal which came back positive. Hence patient was diagnosed with alpha-gal syndrome. After that diagnosis patient continued to be in good health, just that she could not eat any mammalian meat again.

Discussion

AGS was first described in mid 2000s in southeastern United states [1,2] when a number of patients undergoing clinical trials of *cetuximab* (a medication used in patients with squamous-cell carcinoma of the head and neck metastatic colorectal cancer) showed allergic reactions during the first infusion [2]. A few years later multiple reports of hypersensitivity reactions to red meat products surfaced from the United States and Australia which triggered investigation into AGS [3].

As more and more cases of a-Gal syndrome were documented in the United States, a peculiar overlap between the geographic distribution of this syndrome and range of the lone star tick (Figure 1), *Amblyomma Americanum*, was observed [2-4] (Figure 2). *Amblyomma Americanum* also transmits the causative agents of Rocky Mountain spotted fever (*Rickettsia*) and ehrlichiosis (*Ehrlichia*) [3]. Further investigation provided evidence that tick bites from *Amblyomma Americanum* triggers production of specific IgE antibodies and sensitization to the carbohydrate a-Gal [1,5].



Figure 1: Lone star tick. Available from Centers for Disease Control and Prevention in the public domain [6].



Figure 2: Geographic distribution of lone star tick, *Amblyomma americanum*. Available from Centers for Disease Control and Prevention in the public domain [7].

Galactose- α -1,3-galactose (a-Gal) is an oligosaccharide expressed on glycoproteins and glycolipids of non-primate mammal cells [1,5]. These mammals hold a functional GGTA1 gene that encodes for α -1,3-galactosyltransferase [3]. Unlike these mammals, members of Catarrhine primates, namely humans, apes, and old-world monkeys, have lost the ability to synthesize a-Gal [1,3-5]. Inability of humans to produce a-gal makes this carbohydrate immunogenic to them causing production of IgG and IgM antibodies to a-Gal and triggering hyperacute rejection in xenotransplantation (transplantation of animal organs into humans) [4,5].

Association between AGS and tick bites is well established [1-5,8,9] (Figure 3). Ticks are hematophagous ectoparasites of vertebrates some of which have the ability to express toxins in their saliva and/or transmit bacteria, viruses, protozoa, and helminths into a host's, humans or other animals, blood stream [8]. AGS cases have been reported on every continent except Antarctica [3] and while *Amblyomma americanum* has been established as the dominant tick species causing AGS in the United States [1], other species have been associated with AGS in other regions [1,2,4,6] (Table 1).

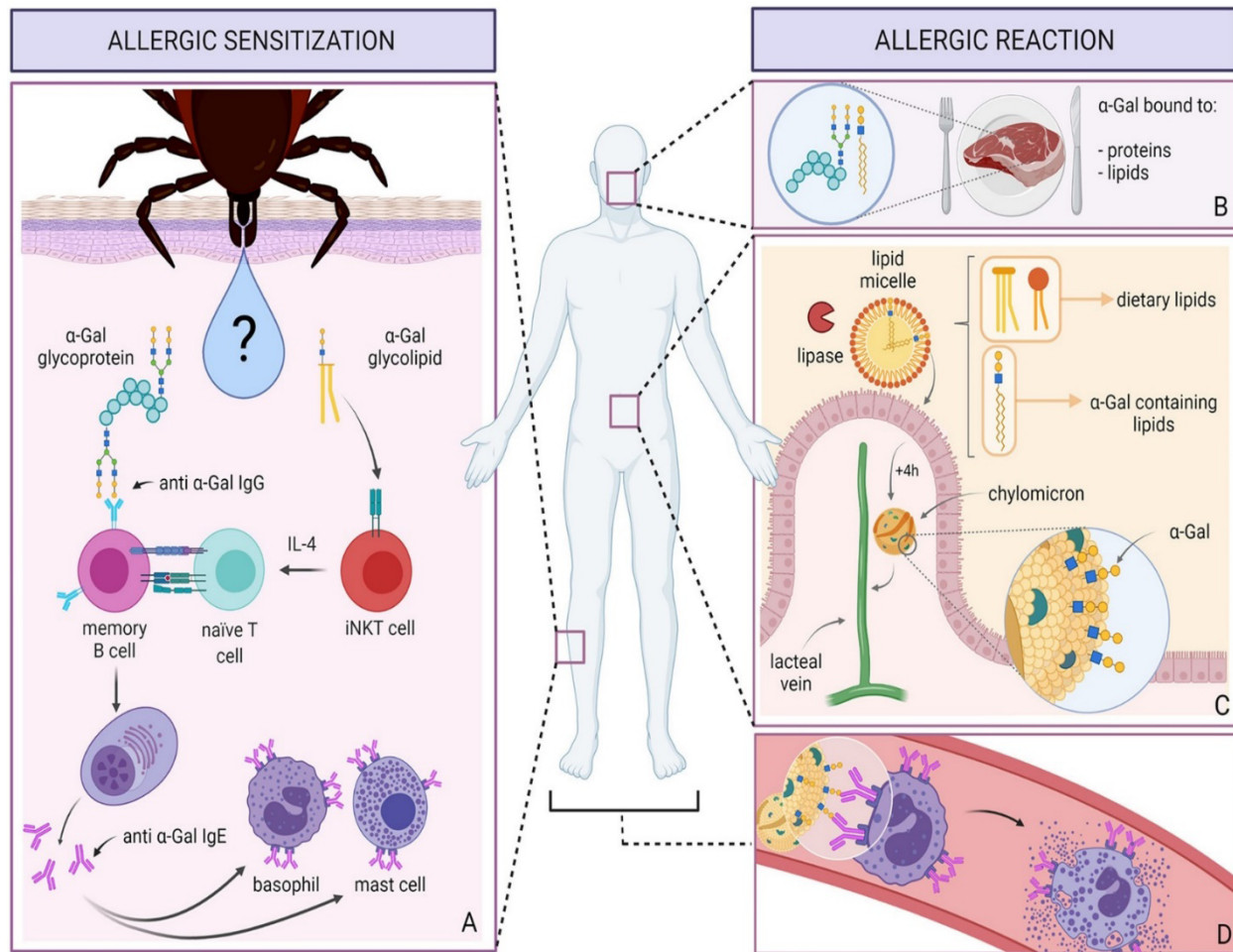


Figure 3: Allergic sensitization to a-Gal [5].

Continent	Suggested associated tick
Africa	<i>Amblyomma variegatum</i>
Asia	<i>Haemaphysalis longicornis</i> , <i>Amblyomma testudinarium</i> , <i>Ixodes nipponensis</i>
Australia	<i>Ixodes holocyclus</i> <i>Ixodes (Endopalpiger) australiensis</i>
Europe	<i>Ixodes Ricinus</i> <i>Rhipicephalus spp.</i>
North America	<i>Amblyomma cajennense</i> <i>Amblyomma americanum</i>
South America	<i>Amblyomma sculptum</i>

Table 1: Tick species associated with AGS across all continents except Antarctica [3].

Consistent with known a-Gal producing sources, the symptoms are primarily observed after consumption of meat from non-carnivore/non-primate mammals, such as beef, pork and lamb [1-5] and reactions to rabbit, buffalo, venison, and kangaroo have also been reported [2]. Most patients will present a positive IgE assay toward cow's milk but can usually tolerate dairy products and milk [1,3,4] and may have less severe/less frequent reaction to gelatin containing food [1]. Furthermore, reactions nonmammalian animal meat such as chicken, turkey, or fish have not been reported [1,4].

Even though delayed hypersensitivity reaction is observed with consumption of red meat, immediate hypersensitivity response is observed with injection of pharmaceutical products that contain alpha-gal [3]. In fact, hypersensitivity reaction to cetuximab, a chimeric mouse-human IgG1 mAb against epidermal growth factor receptor used for used in patients with squamous-cell carcinoma of the head and neck metastatic colorectal cancer [1-3,5] initiated research into AGS. Other examples of pharmaceutical products that may trigger hypersensitivity reaction in individuals with AGS include the measles-mumps-rubella vaccine and zoster virus vaccine, as they contain a significant amount of gelatin, which contains the alpha-gal epitope [1,4]. Hypersensitivity

reaction to other gelatin containing pharmaceutical agents such as Gelofusine, Haemaccel, and vaginal fenticonazole have also been implied [4]. Magnesium stearate (a form of stearic acid) which is used in manufacturing of many drugs (acetaminophen, naproxen, lisinopril, hydrocodone/acetaminophen, clonidine) has also triggered AGS hypersensitivity response [4,10,11].

Symptoms of AGS are similar to other IgE hypersensitivity reaction namely cutaneous manifestations such as hives and rash, gastrointestinal symptoms such as abdominal pain, nausea, and diarrhea, and sometimes dyspnea, dizziness, loss of consciousness and even life threatening anaphylaxis. Symptoms occur a few hours after consumption of allergens or immediately after injection of allergic pharmaceutical agents containing a-Gal [1-5]. However, some patients report a shorter delay and/or more severe reaction with alcohol consumption, exercise, use of Nonsteroidal anti-inflammatory drugs (NSAIDs), or high a-Gal containing food such as pork kidney and sausage casing [4,5].

Unlike other food allergies, in AGS IgE antibodies are produced against a-gal oligosaccharide rather than a protein antigen [3]. Additionally, AGS usually starts in adults or adolescents, but it can develop during childhood [3,5]. AGS is often seen in adults with no atopic disposition [5] who displayed no intolerance to mammalian meat for decades [3]. Furthermore, symptoms of AGS are primarily observed with a delay unlike other IgE mediated food allergies which are immediate and acute [3,5]. Symptoms are typically observed >2 hours after consumption of allergen often ranging between 3 to 8 hours [1-5]. Many patients have awoken from sleep with allergic or anaphylactic symptoms hours after consuming red meat [2]. The precise cause of this delay is unclear [4]. However, this delay in basophilic reaction was not observed upon in vitro exposure of subjects' basophils to a-Gal which suggested neither the properties of oligosaccharide a-Gal nor the responsiveness of basophils are the cause of the delay in symptoms. Therefore, it is proposed that the delay in symptom presentation is due to the delay in appearance of epitope-rich molecules in the blood stream [1,5]. It is suggested that this delay is caused by slower absorption of a-Gal bound lipids via chylomicrons and very low-density lipoproteins [1,2,4,5] (Figure 4).

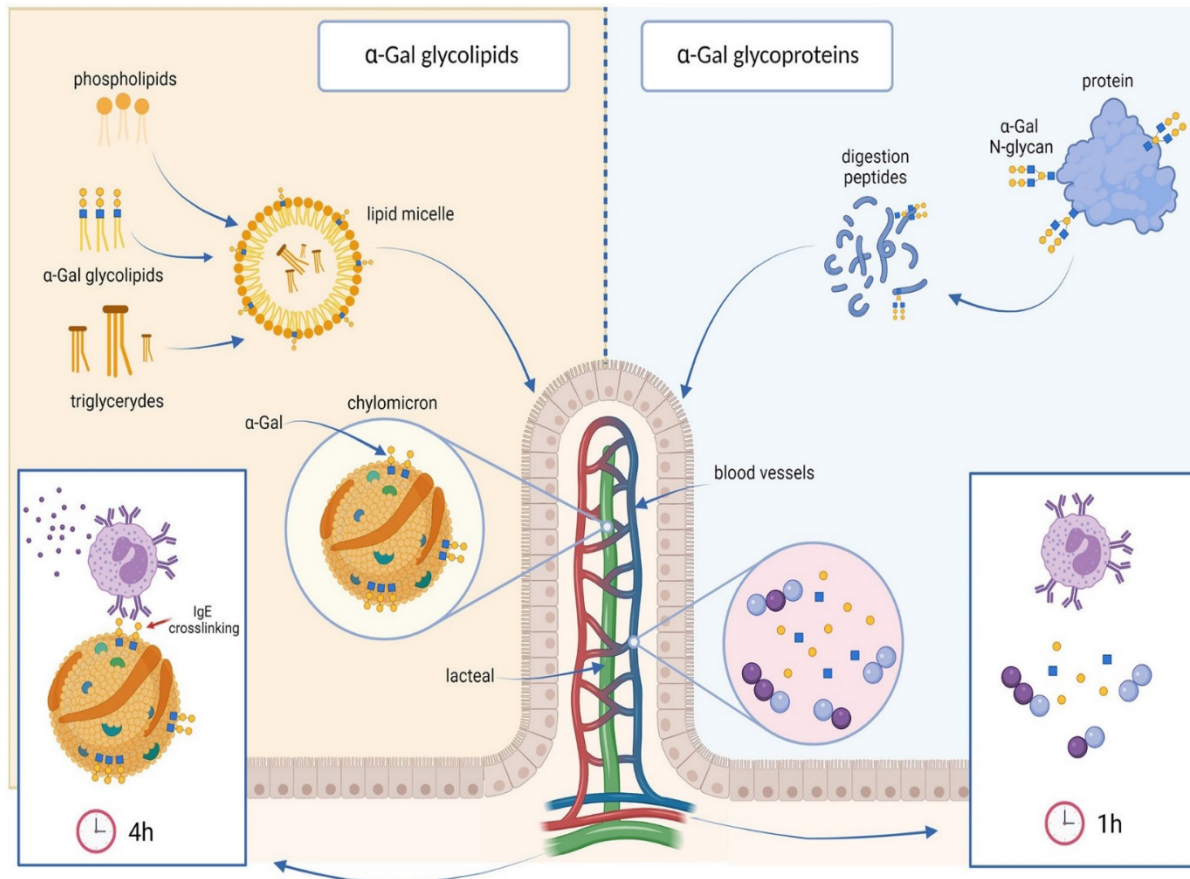


Figure 4: The glycolipid hypothesis [5].

Diagnosis of AGS is done after treatment of hypersensitivity reaction in an outpatient setting as is the case for most hypersensitivity reactions. Patients with AGS produce no or a weak wheal and reactions (2-4mm in diameter) to skin prick tests using commercial extracts of beef, pork, or lamb making this test unreliable for diagnosis of a-Gal allergy and therefore is not recommended [1,2,5]. Currently the most reliable test for diagnosis of a-Gal sensitivity, albeit having questionable clinical correlation when used alone, is in vitro determination of a-Gal specific IgE antibodies in patients' sera using the ImmunoCAP assay [2,5]. A study using this assay in Germany showed elevated IgE levels >0.1 kUA/L against a-Gal in 35% of German forest service employees and hunters who were highly exposed to ticks and in 15% of age-matched control group from the general population and only 5% of a-Gal IgE-positive subjects suffered from a clinical AGS making clinical correlation and definitive diagnosis of the disease solely based on this test limited [5]. Therefore, AGS is diagnosed using the combination of the measurement of serum IgE antibody levels, risk factors, and the clinical presentation of AGS [1,5, 12-14].

Currently there is no definitive cure for AGS. Hypersensitivity reactions are treated based on severity using antihistamin medications and/or epinephrine. Patients are strongly advised to avoid consumption and eliminate red meat and gelatine containing products from their diet [1-3]. Dairy product consumption varies by patients. Some patients may safely consume dairy products but some are advised to avoid them [2]. Patients are also advised to avoid use of certain drugs and vaccination that contain gelatin or other sources of a-Gal [3]. Furthermore, patients are prescribed epinephrine autoinjector and advised to develop home emergency action plan in case of accidental anaphylactic reaction [1-3].

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