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Alpha-Gal Syndrome: A New Etiology for Periorbital Edema

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Abstract: Alpha-gal syndrome is characterized by an IgE-mediated hypersensitivity response to the carbohydrate galactose-alpha-1,3-galactose. It can manifest as both an immediate drug allergy to pharmaceuticals containing alpha-gal as well as a delayed hypersensitivity response to the ingestion of mammalian meat products. In the United States, sensitization to alpha-gal is thought to occur from tick bites and can cause severe angioedema, most commonly periorbitally and periorally, with high rates of anaphylaxis. We present a unique case of chronic periorbital edema in a carnivorous individual after acquiring a new red meat allergy from Alpha-Gal Syndrome.

Alpha-gal syndrome is an immune-mediated hypersensitivity response to the carbohydrate galactose-alpha-1,3-galactose (alpha-gal), a sugar molecule found in nonprimate mammals.^{1–5} It includes both a drug allergy, characterized by immediate hypersensitivity responses to injected pharmaceutical products containing alpha-gal, and a food allergy, characterized by delayed reactions after ingestion of red mammalian meat.^{1–5} Currently, we believe the sensitization begins with a bite from the Lone Star tick (*Amblyomma americanum*), which increases expression of alpha-gal sugar in its saliva after a blood meal from nonprimate mammals such as the deer.^{1–4,6} After a bite, the sugar molecule is transferred to humans, triggering an immune system reaction that later produces mild to severe allergic reactions to red meat such as beef, pork and lamb in 2–6 hours.^{6,7} Immune responses in humans are variable and influenced by cofactors and the dose and form of alpha-gal consumed; however, a majority of patients present with cutaneous symptoms characterized by urticaria, angioedema, and pruritis.^{8,9} Diagnoses can be challenging given

the delayed and variable presentation, particularly in patients with high-consumption of mammalian meat products. We aim to describe this newly recognized entity and shed light in its ophthalmic manifestations. This study adhered to the principles outlined in the Declaration of Helsinki and was HIPAA compliant. The patient consented to publication of identifiable photographs.

CASE REPORT

A 53-year-old male was referred for oculoplastic consultation for chronic periorbital edema and erythema of 1-year duration. He reported recurrent daily episodes of bilateral periorbital edema that lasted several hours with notable worsening at night. Before presentation, he had seen over 5 medical providers and was tried on various treatment regimens including daily antihistamines, oral and topical prednisone, and a daily diary to elucidate any identifiable triggers. Medical history was pertinent for hypertension and benign prostate hyperplasia for which he took a daily aspirin, amlodipine, tamulosin, fish oil, and multivitamin. He denied any known drug allergies. Exam showed bilateral 20/20 visual acuity, normal intraocular pressures, full extraocular movements, bilateral reactive pupils, and a normal dilated fundus exam. External exam was pertinent for significant bilateral nonpitting periorbital edema with malar extension and slight perioral involvement (Fig. 1). His skin was thickened but soft without any notable rashes. Examination of lymph nodes, trunk, and extremities was within normal limits. Angioedema remained highest on differential diagnosis, which also included blepharochalasis syndrome, idiopathic orbital inflammation, histiocytic disorders, and infiltrative conditions among other causes of periorbital and facial edema. Despite extensive questioning, no identifiable triggers could be elucidated; however, he persistently claimed symptoms worsened at night. In consultation with his primary care provider, we discontinued both amlodipine and aspirin as these are common causes of angioedema, but no improvement was noted at 2 months follow up. A maxillofacial CT scan showed soft tissue swelling without any enlarged lymph nodes or masses. A biopsy was taken of left upper eyelid skin and orbicularis muscle, which showed edema and chronic inflammation with normal immunofluorescence and negative IgG4 staining. No foamy histiocytes or loss of elastin fibers were seen, excluding histiocytic disorders and blepharochalasis. The patient was sent for an extensive environmental allergy panel, which was normal. Additional labs were ordered including C4 complement and C1 Esterase Inhibitor, which were normal. After consultation with a second allergist, the patient's report of nocturnal exacerbations prompted a test for serum IgE to galactose-alpha-1,3-galactose. The results were positive, concluding a diagnosis of Alpha-Gal Syndrome.

DISCUSSION

Alpha-gal syndrome is characterized by a constellation of symptoms associated with immune-mediated hypersensitivity responses to galactose-alpha-1,3-galactose. It was first described in 2008 by Chung et al., who observed that cancer patients living in the Southeastern United States experienced significantly more anaphylactic reactions than patients in the Western United States after receiving cetuximab, a cancer chemotherapeutic agent.¹ They found that cetuximab was glycosylated with galactose-alpha-1,3-galactose and when sensitized patients with preexisting IgE antibodies to galactose-alpha-1,3-galactose received the drug, an immediate hypersensitivity reaction occurred.¹ Furthermore, they

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FIG. 1. External photo showing bilateral periorbital edema with malar extension and mild perioral involvement.

noticed these cases clustered in areas with high prevalence of Rocky Mountain spotted fever transmitted by *Amblyomma Americanum* and later showed an association between sensitization to alpha-gal and a history of tick bite.¹ Shortly after in 2009, Commins et al. and Van Nunen et al. published the first case series identifying alpha-gal-specific IgE in patients presenting with allergic symptoms after eating meat who also had history of tick bites.^{2,3} Today, a PubMed search for “Alpha-Gal Syndrome” shows more than 152 results since these original works in 2008. These reports describe delayed allergic reactions characterized by urticaria, facial angioedema, and pruritis in 80% to 90% of individuals with anaphylaxis rates as high as 60% in some studies.^{8,9} It is also believed a gastrointestinal predominant form may also exist.^{8,9} The lone star tick species has been a well-known vector for diseases such as spotted fever group rickettsiosis, human monocytic ehrlichiosis, southern-tick-associated rash illness, tularemia, and Heartland virus infection, but this association with delayed anaphylaxis to red meat is the first example of a blood-feeding ectoparasite causing food allergy in the United States. Some evidence even suggests that alpha-gal possibly originates from the tick itself.^{10,11} A study by Crispell et al. used mass spectrometry, immunoblotting, and immunolocalization to study expression of alpha-gal moieties in the salivary glands and saliva of different ticks, including *A. Americanum*, during different stages of feeding on both human and mammalian blood.¹⁰ The alpha-gal antigens were found on ticks who fed on human blood, which lacks alpha-gal, indicating that an alternative recycling mechanism or mechanism producing alpha-gal might exist in ticks.¹⁰ Unlike normal food allergies which cause immediate symptoms, reactions in alpha-gal syndrome are delayed and inconsistent, making diagnosis challenging as seen in our patient. Diagnosis begins with careful history taking with a high level of clinical suspicion. Many patients will recall tick bites and

complain of worsening symptoms at night, as most are more likely to consume red meat at lunch or dinner. In addition, internal organs such as kidneys, liver, heart, and intestines are thought to be more allergenic due to a higher fat and alpha-gal content and cofactors such as exertion, nonsteroidal anti-inflammatory drugs, and alcohol are thought to lower the threshold for reactions and impact on severity.^{3,5,7} Our patient reported eating red meat daily, particularly at dinner with a glass of wine. After diagnosis, he recalled a history of tick bites, which correlated with onset of symptoms. Diagnosis is confirmed when serum alpha-gal IgE is greater than or equal to 2 IU/mL or more than 2% of the total IgE.^{7–12} Our patient had a serum alpha-gal IgE of 3.1 kU/L (Eurofin Viracor). Treatment is primary avoidance of red meat, which will improve symptoms for 80% of patients.^{5,12,13} In the minority of cases with persistent symptoms, avoidance of all meat products including dairy and gelatin-containing foods is required.^{5,13,14} Patients should also avoid cofactors that lower reactivity threshold and carry epi-pen in case of anaphylaxis. Currently, no studies definitively show whether individuals can “outgrow” alpha-gal allergy and safely resume consumption of mammalian meat.⁵ Kim et al. have shown that alpha-gal allergic individuals who avoid tick bites experience a decline in alpha-gal-specific IgE levels.¹⁴ Thus, some allergists recommend checking alpha-gal-specific IgE and total IgE levels in these patients yearly. Some physicians also recommend discussing reintroducing mammalian products back in the diet if alpha-gal-specific IgE levels have dropped to less than 0.35 kU/L or 2% or less of the total IgE, with no adverse reactions to accidental mammalian meat ingestion or known dairy ingestion.⁵ A 2018 study from the University of Tennessee reported that the ability to diagnose alpha-gal syndrome led to a noticeable drop in the number of idiopathic anaphylaxis cases reported in their center, from 59% in 2006 to 35% in 2018.¹⁵ Despite the ability to diagnose

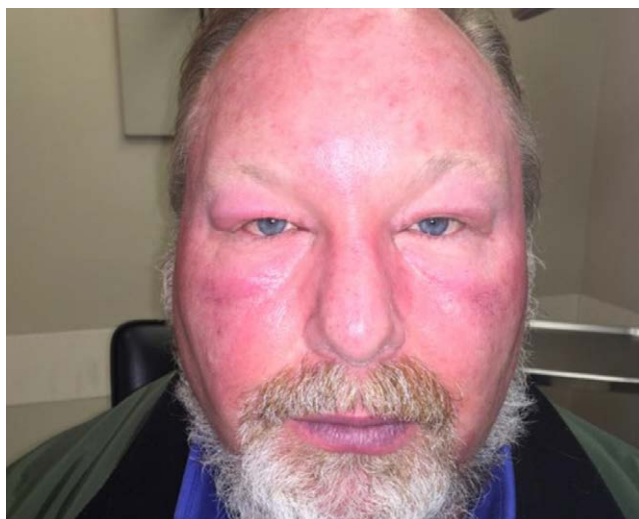


FIG. 2. External photo showing patient with improving periorbital edema after eliminating meat from diet for 3 days.

alpha-gal syndrome, many physicians remain unaware of this growing problem, and patients can often be misdiagnosed. IgE-mediated, delayed allergic reactions to mammalian meat and mammalian products have not commonly been considered as a cause of periorbital edema. However, given the increasingly high rates of sensitization to alpha-gal, particularly in the Southeastern United States, this becomes a clinically relevant and treatable cause of periorbital edema to be considered. We suggest that Alpha-gal syndrome should be added to the differential of periorbital edema particularly for patients in the southeast or with a recent travel or tick-bite history. Our patient was seen 3 days after diagnosis and was noted to have a drastic improvement in symptoms after avoiding consumption of meat products (Fig. 2). He is still safely consuming dairy. As ophthalmologists and oculoplastic surgeons, we can play an important role in diagnosis as evidenced by this case.

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Shewanella algae Causing Pediatric Orbital Abscess With Leptomeningitis

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Abstract: A 13-year-old boy presented with 3 days of left-sided periorbital pain, swelling, mucoid discharge, and fever to 103°F, with onset 1 day after swimming in the ocean. Within 12 hours, he experienced rapid clinical deterioration with formation of a superomedial subperiosteal abscess and

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