ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Alpha-gal syndrome: the first case report from the state of Rio Grande do Norte, northeastern Brazil

Síndrome alfa-gal: primeiro relato de caso do estado do Rio Grande do Norte

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ABSTRACT

We report the first clinical case of alpha-gal syndrome in an older man from the city of Brejinho, in the state of Rio Grande do Norte, northeastern Brazil, along with a brief literature review on the subject. The patient developed delayed anaphylaxis after consuming *buchada de bode* (a traditional Brazilian dish made from goat offal). Living in a rural area, he has frequent contact with tick-infested animals. Alpha-gal syndrome challenges traditional paradigms of food allergy and requires appropriate diagnosis and treatment due to its potentially fatal outcomes. Patients should be advised to avoid mammalian meat and further tick bites, as well as to carry an epinephrine auto-injector for emergencies.

Keywords: Anaphylaxis, viscera, red meat.

RESUMO

Apresentamos a descrição do primeiro caso clínico de síndrome alfa-gal em um idoso da cidade de Brejinho, no estado do Rio Grande do Norte, Brasil, e fizemos uma breve revisão da literatura sobre o tema. O paciente desenvolveu anafilaxia tardia após ingerir uma buchada de bode. Residente em uma zona rural, ele tem contato frequente com animais infestados por carrapatos. A síndrome alfa-gal desafia paradigmas tradicionais de alergia alimentar e requer diagnóstico e tratamento adequados devido aos seus resultados potencialmente fatais. Os pacientes devem ser orientados a evitar carne de mamíferos e novas picadas de carrapatos, além de possuir epinefrina autoinjetável para emergências.

Descritores: Anafilaxia, vísceras, carne vermelha.

Introduction

IgE antibodies specific to oligosaccharide galactose-alpha-1,3-galactose (alpha-gal) have been shown to cause two distinct forms of anaphylaxis in patients previously sensitized by a tick bite — *immediate-onset anaphylaxis*, which occurs after cetuximab use; and *delayed-onset anaphylaxis*, which occurs 3 to 6 hours after ingestion of non-primate mammalian meat (beef, pork, and lamb, hereafter referred to as red meat) —, leading to the diagnosis of an emerging disease called alpha-gal syndrome (AGS). Since then, it has become clear that, as allergists and immunologists, we need to think "outside the box."[1]

AGS appears to challenge several immunological paradigms. For example, anaphylaxis triggered by sensitization to carbohydrates is uncommon compared to reactions caused by protein triggers, and these systemic reactions develop hours after exposure, rather than minutes. Furthermore, reactions seem to

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lack specificity, since they are not to alpha-gal in the tick saliva but rather to the alpha-gal on mammalian meat, and occasionally alpha-gal in non-meat foods and pharmaceuticals. Reactions also tend to subside with strict dietary avoidance, which is unusual for other types of food allergy, especially those acquired in adulthood.[2,3]

For many years, recognition and diagnosis of AGS have been delayed, primarily because neither patients nor physicians have correlated delayed symptoms with the ingestion of red meat. The reasons for delayed onset of symptoms in AGS are not yet fully understood.[4]

This new form of delayed anaphylaxis has been diagnosed more frequently, as evidenced by the series of 2500 clinical cases published by Commins.[2] In Brazil, the most recent case was reported in 2021 by Lima et al.,[5] involving an adolescent from the city of Belém, in the state of Paraíba, northeastern Brazil. A recent review published in January 2024 by Wilson et al. reports fewer than 5 documented cases in Brazil.[6]

This report describes the first clinical case of AGS in an older man from the city of Brejinho, in the state of Rio Grande do Norte, northeastern Brazil.

Case report

A 78-year-old man born and living in Brejinho, Rio Grande do Norte, northeastern Brazil, was admitted to a private clinic for investigation of a clinical suspicion of idiopathic anaphylaxis. The patient reported that, approximately 3 hours after consuming *buchada de bode*, a traditional Brazilian dish made from goat offal, he developed urticarial lesions, bilateral palpebral angioedema, hypotension, dyspnea, and syncope. His family promptly took him to the city hospital, where he had a cardiac arrest and successfully received cardiopulmonary resuscitation. After stabilization, he was transferred to Natal, the capital of the state of Rio Grande do Norte, and admitted to the intensive care unit for 3 days.

The patient denied previous episodes of anaphylaxis, atopy, use of non-steroidal anti-inflammatory drugs, alcohol consumption, intense physical activity, emotional stress, or acute infection that could have acted as cofactors of anaphylaxis. His medical history included hypertension, for which he was taking losartan 50 mg twice daily. Both the patient and his family reported frequent exposure to ticks and tick bites in their residential area. Considering the possibility of AGS, a serum alpha-gal specific IgE test was performed by ELISA, yielding a result of 68.40 kU/L. There is a lack of commercially available specific IgE tests to goat meat or offal components, which highlights the importance and need of regionalizing commercial extracts for allergy testing.

Medical management included advising the patient to avoid red meat and offal products, providing a descriptive medical report on AGS with an emergency action plan, prescribing self-injectable epinephrine, and offering guidance on environmental control to prevent future tick bites.

Discussion

An estimated 7.6% of children and 10.8% of adults have IgE-mediated food-protein allergies in the United States, a condition that may cause anaphylaxis and death. The mortality rate due to food-related anaphylaxis in the United States is estimated at 0.04 deaths per million annually. AGS affects approximately 96,000 to 450,000 individuals in the United States and is currently a leading cause of anaphylaxis in adults. The seroprevalence of sensitization to alpha-gal ranges from 20% to 31% in the southeastern United States.[7]

Genetic susceptibility, changes in the microbiome, skin exposure to detergents, and pollutant exposure are factors that may contribute to the risk of food sensitization and IgE-mediated allergy.[8] For AGS, the most widely studied risk factor is ABO blood group status. The patient in our case report had O+ blood type. Evidence indicates that individuals with B antigen blood group may have some protection against alpha-gal sensitization and/or development of the clinical syndrome, although they can still be affected. Previous studies have shown that alpha-gal differs from the B-group blood antigen by a single fucose at the penultimate galactose residue, a similarity that might be related to the lower risk of alpha-gal sensitization. Male sex, rural residence, and an outdoor lifestyle have been associated with AGS, although these are presumably risk modifiers for tick exposure.[6]

A study in the United States assessed 122,068 serum specimens from 105,674 patients with suspected allergy to mammalian meat and reported an alpha-gal sensitization rate of 32.4%. Individuals aged 70

years and older were most likely to test positive, whereas those aged 0-9 years were the least likely to receive positive test results. Men showed a higher positive test rate than women (43.3% vs. 26.0%). From 2011 to 2018, the number of positive alpha-gal IgE antibody test results increased 6-fold, suggesting a potential rise in alpha-gal sensitization rates in the United States and/or an increase in testing frequency.[9]

A report from the Centers for Disease Control and Prevention (CDC) estimates that between 96,000 and 450,000 persons in the United States might have been affected by AGS since 2010.[10] Reactions to alpha-gal were initially observed in the United States in 2008 in patients treated with cetuximab,[11] a chimeric mouse-human IgG1 antibody containing an alpha-gal glycosylation site on the murine portion.[12] In 2009, a potential association between red meat allergy and tick bite reactions was first suggested in Australia,[13] and in the same year, the first clinical case was described in the United States.[14] In 2011, it was noted that reactions to cetuximab and red meat allergies were occurring in southeastern United States, coinciding with the distribution of the lone star tick (*Amblyomma americanum*).[15] Other tick species have also been associated with AGS, including *Ixodes holocyclus*, *Amblyomma sculptum*, *Ixodes Ricinus*, and *Haemaphysalis longicornis*.[16] Since then, accumulated circumstantial evidence has suggested that tick bites induce alpha-gal-specific IgE, leading to the development of AGS.[17]

Over the past decade, a growing number of studies have expanded the list of possible sensitizing agents leading to AGS. As an emerging disease, there is a crucial need for new information. Areas of uncertainty include understanding whether bites from *A. americanum* and other tick species are indeed the driving sensitizer for AGS. Additional sensitizers have been proposed, such as chigger bites[18] and flea bites.[19] Recently, compelling evidence has also suggested that *Ascaris* infection plays a causative role.[20] Studies exploring the higher rates of *Hymenoptera* venom allergy among patients with AGS have shown that the venom allergens cross-react with tick salivary components, although alpha-gal itself is not one of these cross-reactive antigens. It is not currently clear whether venom allergy is associated with AGS through shared environmental exposures or a direct immunological link, but avoiding stings appears to be important for the resolution of AGS.[21] These new sensitizers support the idea that AGS could be considered an immunoparasitologic syndrome.[3]

AGS is widely recognized as an allergy mediated by alpha-gal-specific IgE antibodies.[14] Humans, great apes, and Old World monkeys do not express alpha-gal; however, it is found in all other mammals, including cows, pigs, and goats.[22] Therefore, humans can be exposed to alpha-gal through the consumption of mammalian meat or products derived from mammals, including pharmaceuticals that contain mammalian components, such as heparin, immunobiological products (such as cetuximab and influenza, measles-mumps-rubella, rabies, varicella, and zoster vaccines),[23] and drugs containing gelatin.[24]

In predisposed individuals, after previous sensitization and subsequent consumption of red meat, delayed allergic reactions can occur, including urticaria, angioedema, gastrointestinal symptoms, or even anaphylaxis. Several theories aim to explain these delayed responses, with the theory involving lipid particles being the most compelling. However, this particular theory is difficult to investigate in humans and has not yet been proven.

The “glycolipid hypothesis” suggests that glycolipid forms of alpha-gal can explain the 3-6 hour delay in symptom onset after ingesting mammalian meat, a delay atypical for IgE-mediated food allergies but characteristic of AGS. This hypothesis is based on the known kinetics of lipid digestion, absorption, packaging, and circulation. Specifically, lipids are packaged into chylomicrons within the intestine and transit via the thoracic duct, entering the systemic circulation approximately 2-3 hours after a fatty meal. Over the subsequent few hours, these lipids progressively transition to smaller lipoprotein particles, such as low-density lipoproteins (LDLs), which are sufficiently small to pass through endothelial walls and enter interstitial tissues where mast cells reside. It is important to note that experimental evidence supporting this hypothesis is currently incomplete, and alternative explanations involving glycoprotein forms of alpha-gal cannot be ruled out. For instance, it is plausible that alpha-gal expression on highly stable proteins, such as collagen and laminin, contributes to delayed digestion and absorption kinetics in vivo.[6]

As observed in the case reported here, the patient developed severe anaphylaxis after consuming *buchada de bode*, a traditional dish from Northeastern

Brazil, culturally representative of the diet of people living in the Brazilian semiarid region (*sertão*), which typically includes goat meat and offal. It is prepared by washing, boiling, cutting, and seasoning goat meat and offal, which are then cooked in bags often made from the goat's stomach. While the name implies goat (*bode*) products, some variations may use offal from lamb, beef, or a combination of different meats.

A serum concentration of alpha-gal-specific IgE of 0.1 kU/L or more supports a diagnosis of AGS in patients who experience delayed allergic symptoms after consuming mammalian meat. In populations with high rates of alpha-gal sensitization, an alpha-gal IgE level of at least 2 kU/L or more than 2% of the total IgE concentration increases the likelihood of a positive mammalian meat oral food challenge (OFC) to greater than 50%.[7]

Diagnosing food allergy requires a detailed clinical history and diagnostic allergy tests, but caution is needed when ordering and interpreting test results to prevent misdiagnosis, which could lead to unnecessary dietary restrictions, expose patients to nutritional risks, and significantly decrease their quality of life. For AGS, skin prick tests using commercial extracts often yield negative or weakly positive results. In these cases, intradermal tests or prick-to-prick testing may be considered, since they demonstrate higher positivity rates.[6] While OFC can be used, its efficacy is limited due to the delayed onset of reactions. When food exclusion is indicated, its subsequent reintroduction should be monitored through an OFC, conducted by a trained specialist in a well-equipped or hospital setting. Food reintroduction at home, without medical supervision, poses risks and should be discouraged.[25]

Management of AGS cases involves advising patients to avoid red meat consumption and tick bites, providing them with an emergency care plan that details medication to use for mild and severe allergic reactions, and prescribing self-injectable epinephrine. Regular clinical follow-up visits are also recommended.[7]

Avoidance of red meat and offal can lead to complete symptom remission in more than 80% of cases, and approximately 5% to 20% of patients may also need to avoid dairy and gelatin. However, some adult patients have regained tolerance to mammalian meat after 1 to 2 years of avoiding additional tick bites.[26,27] It is important to note that the natural course of AGS often involves a reduction in IgE antibody response over time, which can lead to a lower frequency or inconsistency of reactions. Furthermore, patients should be informed that the allergenicity of red meat proteins is preserved even after different thermal cooking methods.[28]

For effective vector control, it is recommended to apply acaricides both to the house and to pets. When exposure to ticks is unavoidable, it is recommended to wear long sleeves, boots, and light-colored long pants to facilitate the visualization of ticks. After use, all clothes should be washed in boiling water for complete tick removal.[27]

Injectable epinephrine is the first-line treatment for severe allergic reactions and/or anaphylaxis. Epinephrine auto-injectors can be used to administer doses in rapid succession (e.g., at 5-minute intervals), which may be necessary to delay the progression of a reaction and reduce the severity of symptoms. A 2021 meta-analysis of 86 studies, including data from 36,557 anaphylactic reactions, showed that 1 in 10 reactions were treated with more than 1 dose of epinephrine, but only 2.2% (95% CI, 1.1%-4.1%) resulted in response failure after 2 doses of epinephrine.[29]

In patients with AGS, serum alpha-gal-specific IgE levels should be regularly monitored, typically every 6 to 18 months.[30] A mammalian meat OFC should be considered when serum alpha-gal-specific IgE levels are below 2 kU/L or less than 2% of the total IgE concentration,[2] although these thresholds may vary according to the population.[31] Strategies to reintroduce mammalian meat into the diet after AGS resolution depend on the patient's and physician's comfort level and should include supervised follow-up.

Oral immunotherapy using cow's milk or beef to treat AGS is still under investigation.[32,33] The development of a Food and Drug Administration (FDA)-approved pig, genetically engineered to not produce alpha-galactosyltransferase enzymes, may provide future avenues for hypoallergenic mammalian meat preparations and enable the use of mammalian products for the treatment of patients with AGS.[34]

Finally, in 2015, Ferreira et al. conducted a systematic review on AGS[27] and reported that, in Brazil, there was only clinical suspicion of this diagnosis. However, as confirmed by this case report, AGS is already present in Brazil and should not be overlooked.

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