



Red Meat Allergy and Castleman's Disease

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Abstract

Background: Anaphylaxis, angioedema or hives have been described after eating red meat. Tick bites are progressively accepted as the sensitizing agent. Castleman's disease is a lymphoproliferative process with different impacts on long-term outcome depending on its centricity. Hyalomma lusitanicum is the most prevalent tick in Castilla-La Mancha.

Methods: Male, 44 years of age, diagnosed with seasonal rhinoconjunctivitis who reported frequent episodes of anaphylaxis in the past six months 4-5 hours after eating meat or offal of lamb. He tolerated beef, pork, venison, wild boar, rabbit and chicken. He acknowledges having been bitten by ticks.

Results: SPT against common aeroallergens: positive for grass and olive pollens. SPT with commercial meats and bovine gelatin-derived colloids (Gelafundin®): negative. IDT with red meats and gelatines: positive. Specific IgE (ImmunoCAP Thermofisher) for meats (lamb 1.54 KU/L, pork 0.82 KU/L, veal 4.94 KU/L), anisakis 14.6 KU/L, ascaris 1.47 KU/L and α-gal 38 KU/L. Spirometry: mixed pattern with bronchodilator response. Chest CT: adenopathy of 13 mm in the left axilla. Lymph node biopsy: compatible with unicentric Castleman's disease, hyaline-vascular type.

Conclusion: We describe two unusual processes in the same patient: delayed anaphylaxis after eating lamb, controlled by exclusion diet, and unicentric Castleman's disease treated with surgical removal of the lymph node. Ticks population in our area differs from ticks in Europe and the north of Europe.

Keywords: Anaphylaxis; α-galactose; Food allergy; Castleman's disease; Lymphoproliferative process

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Introduction

Red meat allergy is a recent [1] condition with scarce cases in Spain [2,3] that can lead to severe reactions (anaphylaxis, urticaria, angioedema), manifested 3-6 hours after intake of red meat of mammals [4,5]. Specific antibodies for galactose-α-1,3-galactose (α-gal) are considered causative agents of the onset of this symptom. In these delayed reactions there are IgE antibodies towards carbohydrates (α-gal) instead of the typical IgE responses to protein epitopes. As red meat allergy has been associated with previous tick bites, the hypothesis that tick bites are the sensitizing event that leads to the development of IgE to α-gal is progressively more accepted [5]. Bovine gelatines contain high amounts of α-gal, so skin tests with gelatin colloids -which show a strong correlation with α-gal IgE ($r = 0.45$) are useful for diagnosis [6].

Case Presentation

We present a male, 44 years of age, owner of a gun store, with a history of seasonal allergic rhinoconjunctivitis to grass pollens and olive and moderate smoker. For the past 6-7 years, he relates episodes of acute urticaria appearing 5-6 hours after eating lamb. In the last month he has had 8-9 episodes, consisting of substernal tightness with dyspnoea, wheezing, weals on legs, thighs and trunk, profuse sweating, hypotonia and abundant loose stool. The symptoms resolved spontaneously in 4-5 hours and were related to meals of lamb meat and offal. He tolerates veal, pork, venison, wild boar, horse, rabbit and chicken.

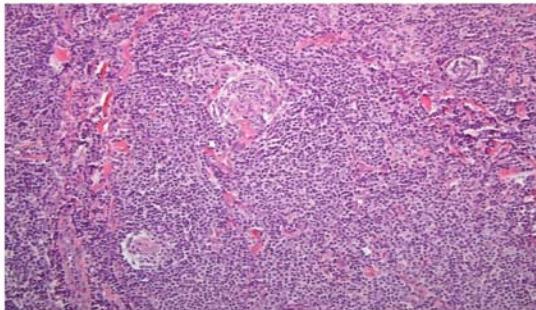


Figure 1: Lymph node injury consisting of follicles of regressive aspect with expanded mantle areas and attenuated germinal centres, with prominence of vessels and intragerminal multiple follicular nests of dendritic cells (CD21+) and nests of perivascular plasmacytoid dendritic cells (CD123+). No aberrant B or T cells population was observed. This is consistent with unicentric Castleman's disease hyaline-vascular type.

The subject goes hunting almost every weekend. He acknowledges having been bitten by ticks and has been hunting for years in "The Garganta", an ecosystem in the south of Ciudad Real (Spain). In this area, the *Hyaloma lusitanicum* is the most prevalent tick (81%) in contrast with the ticks found in the north of Spain and Europe -*Ixodes ricinus*- whose percentage in this ecosystem is 0.2% [7].

For one year he has experienced dyspnoea in response to moderate effort, which he attributed to anxiety. Dyspnoea has progressed daily with night-time awakenings and daytime sleepiness; he is a habitual snorer. Physical examination revealed good general condition without skin lesions, normal blood pressure and cardiopulmonary auscultation and absence of adenopathies.

Blood count, biochemistry panel, serology hepatitis B and C and hydatid disease, C-reactive protein, antinuclear antibodies, thyroid hormones and antithyroid Ab within normal limits. Serum tryptase: 2.5 µg/L. Chest x-ray: normal. Skin prick tests (SPT) with common Aeroallergens against house dust mites, molds, cat and dog dander and pollen: positive for grass pollen and olive. Commercial SPT with pork, lamb, beef and chicken (Bial-Aristegui): negative. Prick-prick with lamb offal: negative. Total IgE: 347 kU/L. Specific IgE (ImmunoCAP ThermoFisher) (kU/L): lamb: 1.54, veal: 4.94, pork: 0.82, rabbit: 0.47, anisakis: 14.6, Ascaris: 1.47, rFel d 1 < 0.35, Pig serum albumin < 0.35, Bos d 6 < 0.35, MUXF3 < 0.35. Immuno-CAP with α-gal-tyroglobulin: 38 kU/L. (Commercial CAP with α-gal was not available at the time of the study).

Intradermal reaction test (IDT) diluted 1/100 with beef, pork, lamb: positive. Undiluted *Gelafundina** (bovine gelatin-derived colloid, 40 mg/mL) was used for SPT and IDT [7]. Only *Gelafundina** IDT was positive (10x11). The *Gelafundina** prick and IDR tests performed in 20 patients with idiopathic anaphylaxis were negative.

The patient stopped eating lamb and there were no more episodes of anaphylaxis except on one occasion when he ate pork bacon. Since then, he has tolerated pork meat, but he avoids pork offal and pork fat.

Basal spirometry: FVC: (62%), FEV1: (50%), FEV1/FVC: 63. After bronchodilator FEV1 improved by 18% (mixed pattern: severe obstructive and restrictive moderate). Spirometry results after treatment with budesonide +formoterol 160/4.5 µg were FVC: (73%), FEV1: (67%), FEV1/FVC: 71, without response to bronchodilators. He was asked to do a one-month gelatin exclusion diet but this did not produce any clinical or spirometric improvement.

As dyspnoea persisted we performed chest CT: 13 mm rounded node in the right axilla with no alterations or vessels in the lung parenchyma. Fine needle aspiration surgery performed on axillary adenopathy was not conclusive for malignancy. Surgery continued with excision biopsy of the lymph node, informed as consistent with unicentric Castleman's disease, hyaline-vascular type (Figure 1). We excluded the presence of other adenopathies after performing neck-thorax-abdomen-pelvis contrast CT.

Conclusion

In conclusion, we describe two rare processes in the same patient:

A) Delayed anaphylaxis to red meat with symptoms after eating lamb and tolerance for other red meat but pork bacon. It was controlled with an exclusion diet. We demonstrated the presence of IgE Ab to red meats and α-gal as well as positive IDR to red meats and *Gelafundina**. Lamb meat was the main trigger of anaphylaxis in our patient, been able to tolerate other red meat containing α-gal epitopes. Other nonallergic factors such as amount consumed at different places, cost or availability could explain that anaphylaxis in other publications was mainly triggered by beef.

Determination of α-gal Ab is the most sensitive and specific technique for the diagnosis of allergy to red meat, followed by IDR testing with gelatines, which although they were positive in the patient did not cause symptoms. However, it is recommended to avoid gelatin colloids.

A background of tick bite is noteworthy in his history where *Hyalomma lusitanicum*, the most prevalent tick in our Meso Mediterranean climate, was the suspected tick. *Ixodes ricinus* species, very frequent in Europe and in the north of Spain has been scarcely found in our area (0.2%) [2,7]. Tick species vary from countries and regions: *Ixodes holocyclus* in Australia, *Amblyoma americanum* in EEUU or *Haemaphysalis longicornis* [8] in Japan. The conditions of scarce humidity and high summer season temperatures in Castilla-La Mancha favor the presence of *H. lusitanicum* throughout the year. So this tick seems the most likely cause of the beginning of anaphylaxis in our patient. We have not found literature about the causal suspicion of *H lusitanicum* in Spain.

There are still many questions to explain in this symptomatology, such as the characteristic delay in onset of symptoms of anaphylaxis, the fact that commercial prick meat extracts are insufficient for the diagnosis of IgE mediated allergy or that patients can tolerate small amounts of meat but they can react with pieces of fat, offal or bacon [4,5].

We think the patient's dyspnoea is related to ACOS syndrome that evolved independently of his red meat allergy.

B) We accidentally discovered an adenopathy corresponding to Castleman's disease with a hyaline vascular pattern which had good response to surgical excision treatment. The radiological whole body scan confirmed that it was unicentric [9,10].

Castleman's disease is an uncommon benign lymphoproliferative disorder of uncertain etiology. Significantly, unicentric forms have a 3 and 5-year survival rates of 90% and 81% respectively compared to 61 and 34% for the multicentric forms. Surgery is the gold standard treatment in unicentric forms. Failure to resect the primarily involved lymph node is the only significant predictor of fatal outcome (17.6 % versus 3.8%).

Our patient is asymptomatic one year after resective surgery. He has undergone clinical examination of all Peripheral lymph node stations with satisfactory results.

The onset of red meat anaphylaxis and Castleman's disease in the same patient seems an isolated association. Current pathogenesis of Castleman's disease might suggest interrelationships between immune system dysregulation, lymphoproliferation, autoimmunity and viruses. We could hypothesize that an environmental trigger (e.g. tick bite or any virus associated to ticks) could stimulate plasmacytoid dendritic cells to produce type 1 interferon and pro-inflammatory cytokines, including interleukin-6. Interferon induces maturation of monocytes into activated antigen-presenting CD that travel to the lymph nodes and tissues, and activate autoreactive T and B lymphocytes. Antibodies that bind nucleic acids and chromatin derived from apoptotic material form immune complexes that stimulate further interferon and pro-inflammatory cytokine production [11]". However, more cases should be reported to explain common pathogenic mechanisms.

These rare pathologies are controlled with a timely and appropriate diagnosis. We believe that a thorough study of the peculiarities of this patient illustrates them and, thus, clinicians should keep them in mind to avoid under-diagnosis given their potential severity.

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