Delayed Anaphylaxis to Red Meat Associated With Specific IgE Antibodies to Galactose

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A novel delayed anaphylactic reaction to red meat, associated with tick bites and IgE antibodies against galactose-α-1, 3-galactose (α-gal), was reported in 2009 in the US, Australia and Europe. In this case, serum specific IgE to galactose-α-1, 3-galactose (> 100 kU/L) and IgE to multiple non-primate mammalian proteins were positive. However, the pathogenesis of this disease remains unclear. We report the first case in Asia of delayed anaphylactic reaction to red meat, which was induced by bites from the hard tick, Hematophagous ixodidae. We confirmed the increased concentration of IgE reactive epitopes in non-primate mammalian organs, which may be rich in α-gal proteins in lymphatic and endothelial tissues. All confirmed ticks associated with this disorder in the literature and in our case belonged to the hard tick family. We hypothesize that hard tick saliva is enriched with blood-type substances, such as oligosaccharides, from the non-primate mammal victim’s blood after days to weeks of blood sucking, which sensitizes humans through the injection route while blood sucking.

Key Words: Food allergy; anaphylaxis; red meat allergy; tick

INTRODUCTION

A novel delayed anaphylactic reaction to red meat was first reported in 2009 in the US, Australia and Europe. This phenomenon was related to tick bites, which are thought to induce IgE antibodies against galactose-α-1,3-galactose (α-gal).1-3 However, the pathogenesis of this disease remains unclear. Here, we report a case of delayed anaphylaxis to red meat with sensitization to α-gal and various non-primate mammalian proteins. To our knowledge, this is the first case of delayed anaphylactic reaction to red meat in Asia.

CASE REPORT

A 56-year-old female visited our clinic with primary complaints of urticaria and anaphylaxis at midnight on 2 occasions. Two weeks before this presentation, she experienced hives with intensive itch and slight palpitations with normal blood pressure at 11 pm. She denied dyspnea or disturbance of consciousness and reacted well to dexamethasone (5 mg) and diphenhydramine (20 mg) intramuscularly. She had eaten 4 hours before the reaction and denied any changes in diet. Three days before her appointment, she experienced a second episode at midnight. Extensive itchy hives rapidly extended from the buttocks to all over the body. She was administered a tablet of cetirizine (10 mg) and felt the urge to have a bowel movement. She showed dizziness, palpitation, hyperhidrosis, chest tightness and dyspnea soon after defecation. She was extremely fatigued and experienced a feeling of impending death, and lost consciousness subsequently. She was sent to the emergency room and her blood pressure was measured as 70/30 mmHg. She reacted well to epinephrine (0.5 mL) intramuscularly and methylprednisolone (40 mg) intravenously. She had eaten 5 hours prior to this reaction. The meal included chicken, eggs, pork, corn, wheat, millet, eggplant, tomatoes and onions. She denied intake of alcohol, seafood or any medicines prior to the episode. She had previously been diagnosed with infiltrating duc-
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The patient was diagnosed with delayed anaphylaxis to red meat according to the history, skin tests, serological tests, and native carcinoma of the right breast and had been treated with surgery followed by radiotherapy, as well as chemotherapy consisting of vinorelbine and capcitabine, which were stopped 7 months before the anaphylaxis attacks. She had no history of monoclonal antibody therapy, including with cetuximab. She lived near farmland with cattle and outdoor dogs. There was no history of allergy, asthma, rhinitis, metabolic disorders, or cardiovascular disease.

Complete blood count, biochemical test panel, complement fractions C3 and C4, antinuclear antibody and tryptase levels were normal. Intracutaneous allergen skin tests to a food panel were negative, except for cow’s milk, pork, beef and lamb (Fig. 1).

Fluorezymeimmunoassay results for IgE were as follows (ImmunoCAP, Phadia, Sweden): total-IgE 276 kU/L, pork (15.4 kU/L), beef (1.98 kU/L), rabbit meat (2.29 kU/L), cow’s milk (3.62 kU/L), dog dander (1.19 kU/L), cat dander (1.30 kU/L), and rat proteins (0.40 kU/L). IgE to mites, a mold mixture panel, and a spring pollen mixture panel including birch pollen, shrimp, chicken, maize, millet, rice, wheat and gluten were all negative. Specific IgE to α-gal was strongly positive (>100 kU/L). Bovine thyroglobulin served as the antigen absorbed in the solid phase in the assay.

Previous studies have shown that fresh extracts of red meat contain more α-gal epitopes than commercial extracts, and hence may produce better skin test results. In addition, non-primate mammalian organs such as kidney contain a higher content of α-gal epitopes, which may contribute to the severity of anaphylactic reactions. Western blotting was performed to analyze the antigen-binding characteristics of serum specific IgE antibodies with pork, organs and bovine thyroglobulin using sera from the patient and a negative control. Lane M: molecular weight markers. Lane A1, B1, C1, D1, E1, F1, G1: protein profiles of pork extracts, porcine liver, porcine kidney, bovine kidney, bovine heart, and bovine thyroglobulin, respectively (Amido Black 10B staining of the blotted membrane following SDS-PAGE performed on a 12.5% polyacrylamide gel with 20 µg of samples in each lane). Lanes A2, B2, C2, D2, E2, F2, G2: Immunoblotting patterns of protein extracts with molecular weights of 52, 68, 90, 140, and 165 kDa (as shown in lane G3), were thought to contain high levels of α-gal epitopes in organs. This may be due to increased expression of α-gal epitopes in lymphatic and endothelial tissue, which are prevalent in organ meat. The pork protein bound to the patient serum (lane A3) at 40, 80, and 120 kDa, similar to a previous study that identified five major groups of molecules with α-gal structures in pig lymphocytes and endothelial cells. The specific IgE binding proteins from denatured bovine thyroglobulin, with molecular weights of 52, 68, 90, 140, and 165 kDa (as shown in lane G3), were thought to contain high levels of α-gal epitopes that could induce high levels of specific IgE to α-gal (>100 kU/L) compared to the moderate levels of specific IgE to pork or beef in the ImmunoCAP assay.

Based on the questionnaire on tick bites, the patient noticed ticks on the dogs and cattle on her farm and had been bitten ~2-3 weeks before the first attack of anaphylaxis; large local reactions resulted, which healed with topical corticosteroid treatment. Some ticks parasitic on her dogs were captured upon request, which were identified as Haemaphysalis longicornis, one of the most common Hematophagous tickidae in north China (Fig. 3).

The patient was diagnosed with delayed anaphylaxis to red meat according to the history, skin tests, serological tests, and...
immunoblotting. Antihistamine and adrenaline, as well as a medical recommendation to avoid red meat, were given. During the 2-year follow-up, she reported mild urticaria several hours after exposure to red meat twice—once after an unexpected intake of pork and once after “a bite of” bovine organs. She reacted well to oral antihistamine without an ER visit. The reason for the recurrence was unexpected exposure and unawareness of cross reactivity.

DISCUSSION

It remains unclear how tick bites induce α-gal sensitization and how delayed anaphylaxis can be triggered by consumption of meat containing α-gal. According to the 32 confirmed cases of tick bite-induced IgE antibodies against 1,3-galacto-(α-gal)-gal, the suspected ticks are Amblyomma americanum, Ixodes holocyclus, and Ixodes ricinus, which all belong to the family Ixodidae (hard ticks).1-3,7,8 The culprit ticks in this case were also hard ticks, which are unique among bloodfeeders for their prolonged feeding period of several days to 2 weeks, during which time the ticks secrete saliva rich in antihemostatic agent to evade the host’s defense mechanisms.9 We hypothesize that tick saliva may be contaminated with oligosaccharides from non-primate mammal blood, which is obtained during blood sucking. In this report, the patient became sensitized to α-gal through the “injection” route by tick bites since she had a history of tick bites but had never received monoclonal antibody therapy, such as with cetuximab (with α-gal located on the Fab portion). Ticks are known to serve as vectors for the pathogen that causes Lyme disease or tick-borne encephalitis; based on these results, ticks may also serve as a “vector” of α-gal, the blood-type substance of oligosaccharides, into humans.

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