

# Beef-Induced Anaphylaxis Confirmed by the Basophil Activation Test

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Beef allergies are relatively rare, especially in adults. However, clinical manifestations can vary from urticaria, angioedema, anaphylaxis to gastrointestinal symptoms. Currently available tests, such as skin testing or in vitro determination of beef-specific immunoglobulin E (IgE), do not provide an accurate diagnosis of beef allergy. The recent development of the basophil activation test (BAT) presents a new opportunity for the diagnosis of food allergies. Here, we report a 37-year-old woman with a history of recurrent generalised urticaria, nausea, vomiting and hypotension after ingestion of beef, suggesting a beef allergy. Although the skin prick test and serum specific IgE to beef, pork and milk allergens showed negative results using commercial kits, the BAT showed significant upregulation of CD203c in a dose-dependent manner compared to both non-atopic and atopic controls. To our knowledge, this is the first case study of beef allergy consisting of a non-IgE-mediated reaction. The detection of food allergies using direct basophil activation is suggested to complement conventional diagnostic tests.

**Key Words:** Beef allergy; basophil activation test; CD203c, human

## INTRODUCTION

Beef allergy is a rare food allergy in both children and adults. Studies regarding this particular allergy have demonstrated a predilection toward atopic dermatitis among children.<sup>1,2</sup> A previous report described 10 cases of food allergy caused by beef in adults, presenting various clinical manifestations, including urticaria, angioedema, anaphylaxis and gastrointestinal symptoms.<sup>3,4</sup> Although the pathogenic mechanisms have not been completely elucidated, previous studies have suggested an immunoglobulin E (IgE) mediated mechanism as being responsible for several clinical manifestations.<sup>1,2</sup>

We report a case of anaphylaxis induced by beef ingestion, suggesting a non-IgE mediated mechanism of beef allergy.

## CASE REPORT

A 37-year-old woman was referred to our allergy clinic for generalized urticaria, nausea, abdominal pain and hypotension one hour after consuming a bowl of beef soup. Prior to this episode, she had experienced generalized urticaria and abdominal discomfort several times after eating grilled beef and pork, which had been treated with intravenous steroids and antihistamine at local emergency centers. She had been able to consume milk, chicken, eggs and fish without any difficulties

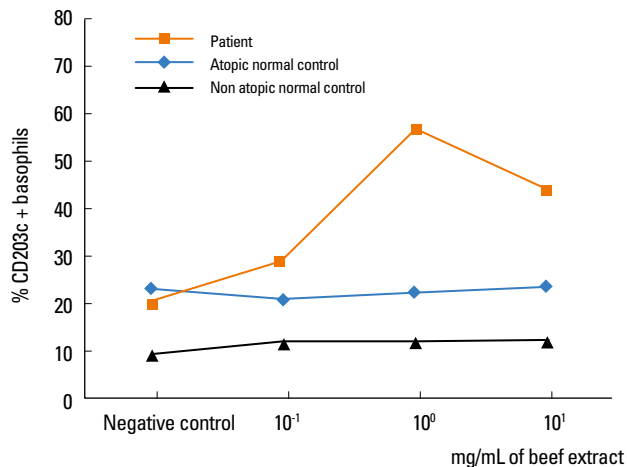
for three years. She was also atopic with positive responses to house dust mites, tree and weed pollens, based on the skin prick test, and was previously diagnosed with allergic rhinitis. To exclude the possibility of food additive hypersensitivity, oral challenge tests with sulfite (200 mg) and sodium benzoate (400 mg) were performed and the results were negative. The results of the skin prick test conducted with a panel of commercial food reagents (Bencard Co., Brentford, UK), homemade raw extracts of beef, pork, milk and bovine serum albumin (New England Biolabs, Hitchin, Hertfordshire, UK) were negative against all allergens tested. Serum specific IgE antibodies to beef, pork and milk allergens measured by the ImmunoCAP system (Phadia, Uppsala, Sweden) showed negative results (<0.35 KU/L). To confirm basophil activation status, flow cytometric analysis (FACScantoII; BD Immunocytometry Systems, San Jose, CA, USA) for activated basophils was performed using allophycocyanin (APC)-conjugated anti-HLA-DR, fluorescein isothiocyanate (FITC)-conjugated anti-CD123 and phycoerythrin-conju-

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**Figure.** Expression of CD203c in basophils induced by beef extract in the patient and control individuals. Controls consist of one healthy subject and one atopic subject suffering from inhalant allergen.

gated anti-CD203c (Immunotech-Beckman Coulter, Marseille, France) triple labelling. The patient's basophils were incubated with various concentrations of beef extracts (0.1-10 mg/mL), anti-IgE antibody (1 µg/mL, Sigma Co., St. Louis, MO, USA) as a positive control and without any drug as a negative control. To exclude nonspecific activation of basophils, two control individuals were included. Following incubation with beef extracts, the patient's basophils showed clear dose-dependent upregulation from 20.4% (spontaneous CD203c expression) to more than 56.9% for 1 mg/mL beef extract (Figure.), whereas the CD203c expression in basophils from the two control individuals remained unchanged (<10%).

The patient was thus diagnosed to have a beef allergy and the patient's resulting avoidance of foods containing beef ingredients has resulted in a remission of urticaria and anaphylaxis.

## DISCUSSION

Beef allergy has been considered a rare food allergy and the pathogenic mechanism has been unknown. Previous studies suggested an IgE-mediated reaction as the pathogenic mechanism in beef allergy and have identified several causative proteins as major allergens, including Bos d 6, Bos d 7, Gal d 5<sup>1</sup> and α-gal.<sup>5</sup> However, there are common discrepancies among these studies with regard to their clinical histories, results from skin prick tests and serum specific IgE. A double-blind, placebo-controlled food challenge was advocated as the gold standard to diagnose food allergy. However, it cannot be easily performed in patients with food-induced anaphylaxis for practical and ethical reasons. If the serum specific IgE is undetectable, as in this patient, no methods are available to confirm the beef allergy and, thus, elucidate the underlying mechanism.

There have been several reports describing the use of the ba-

sophil activation test (BAT), which is based on the expression or upregulation of CD63 and CD203c.<sup>6,7</sup> The application of BAT for diagnosing food allergies may complement conventional tests.<sup>8</sup> Basophils can be activated by a number of stimuli, which are mediated by the high-affinity IgE receptor (FcεRI) or distinct activation pathways, such as the complement system or pharmacological agents. BAT has been used to diagnose pollen-associated food allergies, egg allergies and peanut allergies, suggesting that it is an effective tool for food allergy diagnosis.<sup>9</sup> In the present case study, BAT results were relevant to the clinical history of the patient, showing upregulation of CD203c from 20.4% to 56.9% following incubation with 1 mg/mL of beef extract.

CD203c has recently been evaluated as a marker of basophil activation.<sup>10</sup> In comparison with CD63, CD203c was expressed only in basophils, suggesting that no additional marker is required to monitor basophil activation. Moreover, the detection of CD203c expression does not require preincubation with interleukin-3 (IL-3) and the anti-IgE antibody conjugate. The upregulation of CD203c is not restricted to FcεRI-induced signalling but, rather, is mediated by other signalling pathways, such as IL-3 or tetradecanoyl phorbol acetate (TPA), which is a stimulator of the protein kinase C (PKC) pathway.<sup>10</sup> A previous study documented the extremely rapid TPA-mediated upregulation of CD203c and increase in PKC activity in the colonic mucosa after consumption of beef.<sup>11</sup> Therefore, the symptoms in the present case could have been due to a non-IgE-mediated reaction with direct basophil activation due to the beef allergen.

In conclusion, using BAT, we confirmed a mechanism of beef-induced non-IgE-mediated anaphylaxis in a patient.

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