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Letter to the Editor

Anaphylaxis in a pectin- and cashew nut-allergic child caused by a citrus bath

Dear Editor,

Infants and children with severe eczema and/or egg allergy have a higher risk of tree nut allergies,¹ among which, it is well known that cashew nut cross-react with pistachio nut.² A recent study reported an allergic association between cashew nut and pectin or citrus fruits.³ Here, we report a case that had type-1 allergy to cashew nut and pectin who developed severe anaphylaxis after a citrus bath. A 7-year-old boy presented to an emergency room complaining of generalized wheals and dyspnea after 5–10 min of bathing with Japanese citrus (yuzu) bath additives (Fig. 1a, b). Pediatricians diagnosed anaphylaxis and administered an intramuscular injection of epinephrine. Then, he was referred to a dermatology clinic to determine the culprit allergens. He had a complication of atopic dermatitis and a history of anaphylaxis caused by cashew nuts. His symptom of atopic dermatitis was moderate disease (score 3) according to investigator's global assessment. His parents had eaten cashew nuts at home and also made homemade seasonings with yuzu. He also experienced itchy oral discomfort when he drank a pectin-containing fermented milk product. Because cross-sensitization among cashew nut, pectin, and citrus fruits had been reported,³ we suspected the transdermal allergic reaction to yuzu bath additives. We performed a skin prick test that revealed strong reactions to cashew nuts, pistachios, yuzu endocarp, ingredients in the bath additives, pectin from citrus (from Nacalai Tesque, Kyoto, Japan), and a pectin-containing fermented milk product (from Yakult Honsha, Tokyo, Japan) (Fig. 1c). He had high allergen-specific IgE levels for cashew nut component Ana o 3 (19.6 UA/mL) and crude cashew nut (9.62 UA/mL) by ImmunoCAP® test, although his non-specific IgE was 144 IU/mL.

To confirm anaphylaxis had been caused through IgE-mediated reaction, we performed a basophil-activation test⁴ by using the Allergen Kit (Beckman Coulter, Fullerton, CA, USA) for the quantification of basophil CD203c expression. As expected, the incubation of his blood, but not that of a healthy subject, with yuzu additives, pectin, or cashew nuts increased the number of CD203c^{high} basophils *in vitro* (Supplementary Fig. 1).

To assess the culprit allergen in citrus, we performed a Western blot (WB) assay and found a band specific for the endocarp of yuzu reacting with the patient's IgE, but not the exocarp or flesh of the

fruit (Supplementary Fig. 2, area within dotted line). Because pectin is mainly contained in the endocarp of citrus fruit, this result is consistent with pectin allergy. Furthermore, the bands found in the WB assay in dotted line were smeared, suggesting the allergen comprises a mixture of various molecular weights. In addition, to assess potential cross-reactivity among yuzu, cashew nuts, and pectin, we performed an inhibition test using an enzyme-linked immunosorbent assay (ELISA). The patient had specific IgE to cashew nut, but this reactivity was inhibited by the addition of cashew nuts and pectin (Fig. 2a). The reactivity was reduced to almost zero when inhibited by cashew nuts, whereas pectin blocked 25 % of the reactivity. Of note, our case had specific IgE to the endocarp of yuzu, bath additives containing yuzu extracts, and pectin (Fig. 2b). Interestingly, the IgE reactivity to cashew nuts was completely inhibited by the addition of cashew nuts themselves, whereas it was partially inhibited by the addition of pectin. Also, we showed that IgE reactions to the endocarp of yuzu were completely inhibited by pectin and cashew nuts.

Pectin is a structural heteropolysaccharide found in the cell walls of vegetables and fruits such as citrus, apple, and sugar beet pulp.⁵ Pectin is often added to fermented dairy drinks because of its stabilizing effect.⁶ Räsänen *et al.*, reported the first case study of cross-reactivity between pectin and cashew nut allergy in 1998.⁷ Ferdman reported a possible association among pectin, cashew nut, and pistachio.³ In general, allergy to cashew nut usually cross-reacts with pistachio.² Our study revealed that allergens in yuzu or pectin partially cross-reacted with cashew nut. We hypothesized that the main allergen of cashew nut, Ana o 3 (14 kDa), does not cross-react with yuzu or pectin because of the difference in their molecular weights. We assume that another allergen of 50–80 kDa (by WB assay) has cross-reactivity with cashew nut, yuzu, and pectin. Of note, specific IgE in previously reported Japanese cases of *Citrus unshiu* allergy bound to a 50–70 kDa fragment.⁸ The reported allergen component in cashew nut is Ana o 1⁹, with a molecular weight of approximately 50 kDa; however, we have no data to prove cross-reactivity between Ana o 1 and citrus allergens. In a study of patients allergic to cashew nut, WB assay showed strong IgE binding to Ana o 1 in three patients and weak binding in seven patients.⁹ This suggests that a small number of patients with cashew nut allergy might also be allergic to yuzu and pectin.

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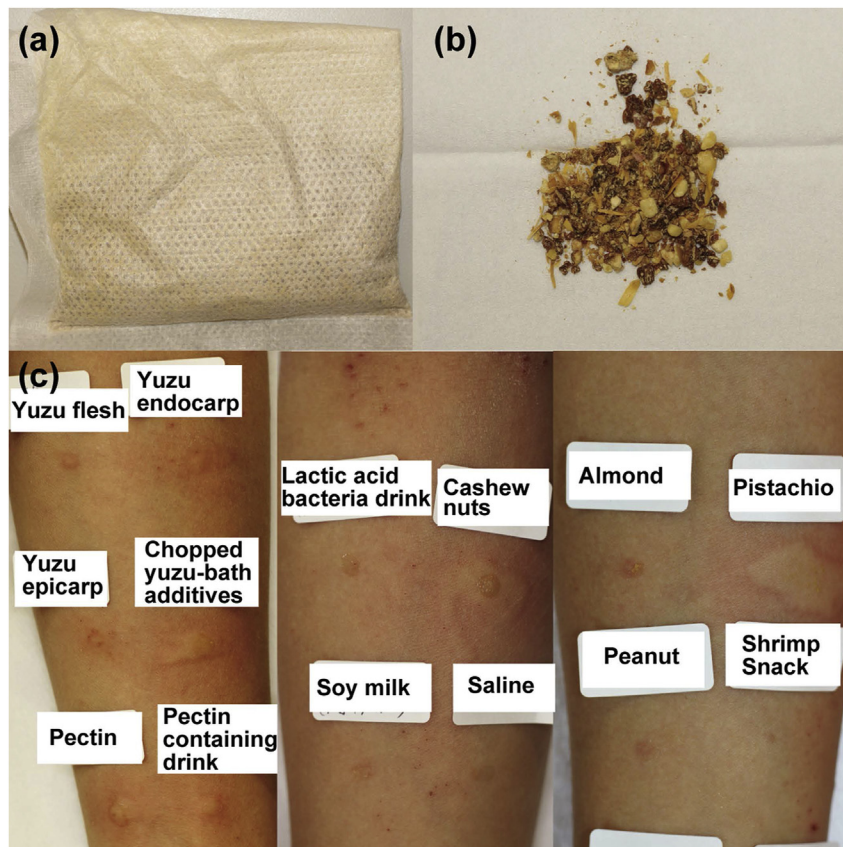


Fig. 1. Skin prick test with yuzu bath additives. (a) Cloth bags used by the patient with (b) bath additives containing dried and chopped whole yuzu, which included freeze-dried yuzu ingredients including the endocarp, exocarp, and flesh. (c) Skin prick test was positive for yuzu endocarp, chopped yuzu-bath additives, pectin, pectin-containing drink, cashew nuts, and pistachios. However, it was negative for yuzu flesh, yuzu epicarp, lactic acid bacteria drink, soy milk, almond, peanut, and shrimp snack.

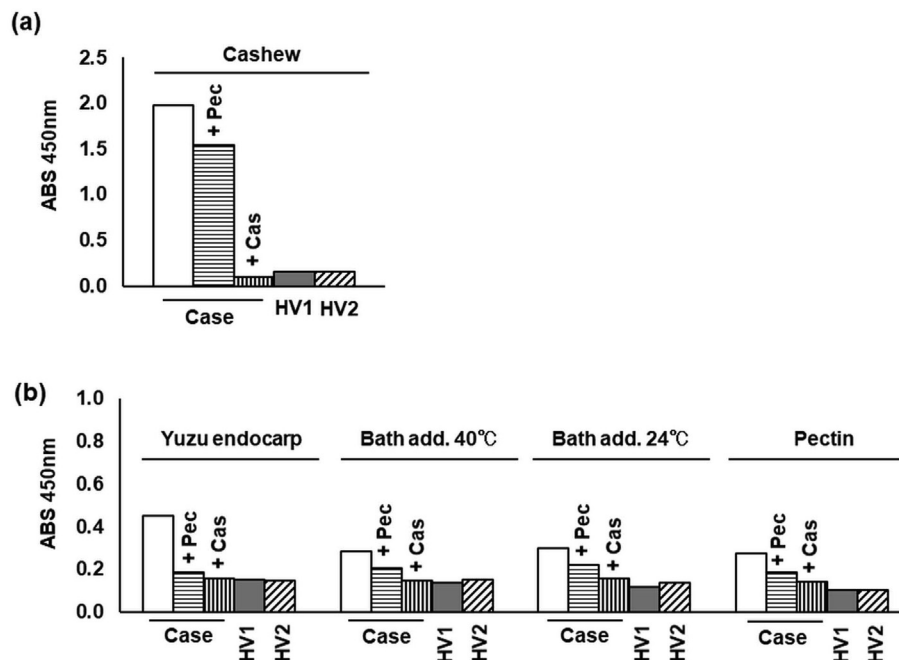


Fig. 2. Inhibition ELISA. (a) Binding of serum IgE from the patient to cashew was partially inhibited by the addition of pectin (+pec), and fully inhibited by the addition of cashew itself (+cas). For controls, sera from two healthy volunteers (HV1 and HV2) were compared. (b) Binding of serum IgE from the patient to the endocarp of yuzu was completely inhibited by the addition of pectin (+pec) or cashew nuts (+cas). For controls, sera from two healthy volunteers (HV1 and HV2) were compared. Yuzu bath additives (Bath add.) were extracted and diluted in water at 40 °C or 24 °C. The difference in extraction temperature resulted in little change for the IgE reactivity to the bath additives.

We present a case of anaphylaxis, caused by yuzu bath additives. Taking a citrus bath is a Japanese health practice in winter. However, we do not recommend these baths for people with an allergy to pectin, cashew nut, or pistachio. Our patient also complained of itchy oral discomfort when he drank a fermented dairy product, because it contained pectin. Therefore, pectin-containing beverages might also be a risk for people with an allergy to pectin, cashew nut, or pistachio. To the best of our knowledge, this is the first study to report anaphylaxis induced by yuzu bath additives, probably due to transdermal contact to allergens. After the patient was advised to avoid allergens as discussed above, he developed no additional allergic reactions.

In conclusion, we showed partial cross-reactivity between cashew nut and pectin or yuzu, although our data are limited because this is a case report. Furthermore, we did not perform absorption spectrochemical analyses to prove the culprit allergen was Ana o 1, because the smear-like bands obtained on WB were relatively weak. We assume that a small number of patients with cashew nut allergy are also allergic to yuzu or pectin. Such patients should avoid contact with pectin including drinking, inhalation, or contact by bathing.

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This study protocol was approved by the Ethics Committee at Kobe University Graduate School of Medicine (No. 180186).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.07.006>.

Conflict of interest

MN and NS are employed by Hoyu and KaM belongs to an endowed department affiliated to Hoyu. The rest of the authors have no conflict of interest.

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References

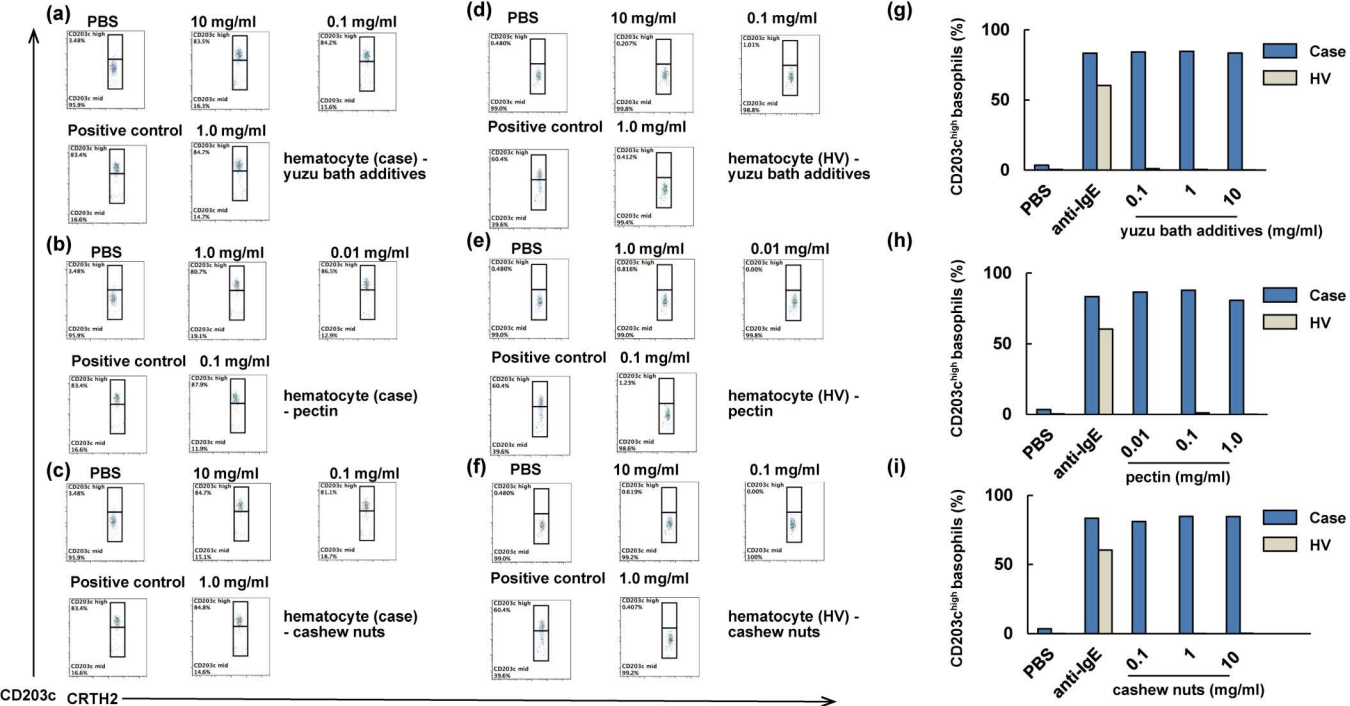
- Stiefel G, Anagnostou K, Boyle RJ, Brathwaite N, Ewan P, Fox AT, et al. BSACI guideline for the diagnosis and management of peanut and tree nut allergy. *Clin Exp Allergy* 2017;**47**:719–39.
- Savvatanos S, Konstantinopoulos AP, Borga A, Stavroulakis G, Lidholm J, Borres MP, et al. Sensitization to cashew nut 2S albumin, Ana o 3, is highly predictive of cashew and pistachio allergy in Greek children. *J Allergy Clin Immunol* 2015;**136**:192–4.
- Ferdman RM, Ong PY, Church JA. Pectin anaphylaxis and possible association with cashew allergy. *Ann Allergy Asthma Immunol* 2006;**97**:759–60.
- Oda Y, Washio K, Fukunaga A, Imamura S, Hatakeyama M, Ogura K, et al. Clinical utility of the basophil activation test in the diagnosis of sweat allergy. *Allergol Int* 2020;**69**:261–7.
- Muñoz-Labrador A, Moreno R, Villamiel M, Montilla A. Preparation of citrus pectin gels by power ultrasound and its application as an edible coating in strawberries. *J Sci Food Agric* 2018;**98**:4866–75.
- Kiani H, Mousavi ME, Mousavi ZE. Particle stability in dilute fermented dairy drinks: formation of fluid gel and impact on rheological properties. *Food Sci Technol Int* 2010;**16**:543–51.
- Räsänen L, Mäkinen-Kiljunen S, Harvima RJ. Pectin and cashew nut allergy: cross-reacting allergens? *Allergy* 1998;**53**:626–8.
- Tanaka Y, Sugihara M, Tsumagari S, Takamatsu N, Kurihara K. [Food-dependent exercise-induced anaphylaxis due to ingestion of mikan (Citrus Unshiu)]. *Arerugi* 2017;**66**:1011–5 (in Japanese).
- Wang F, Robotham JM, Teuber SS, Tawde P, Sathe SK, Roux KH. Ana o 1, a cashew (*Anacardium Occidentale*) allergen of the vicilin seed storage protein family. *J Allergy Clin Immunol* 2002;**110**:160–6.

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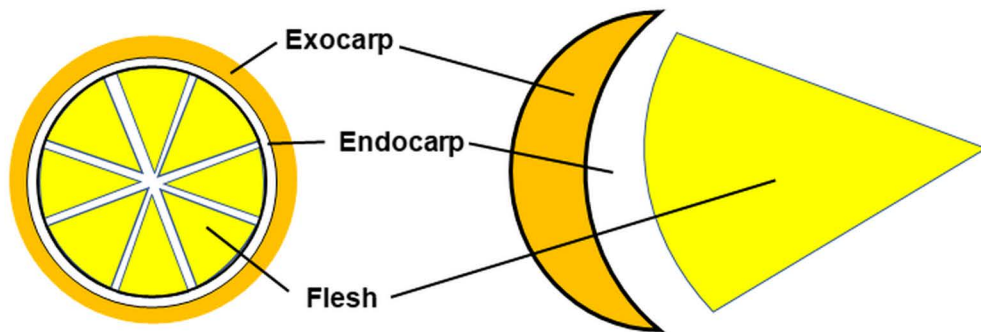
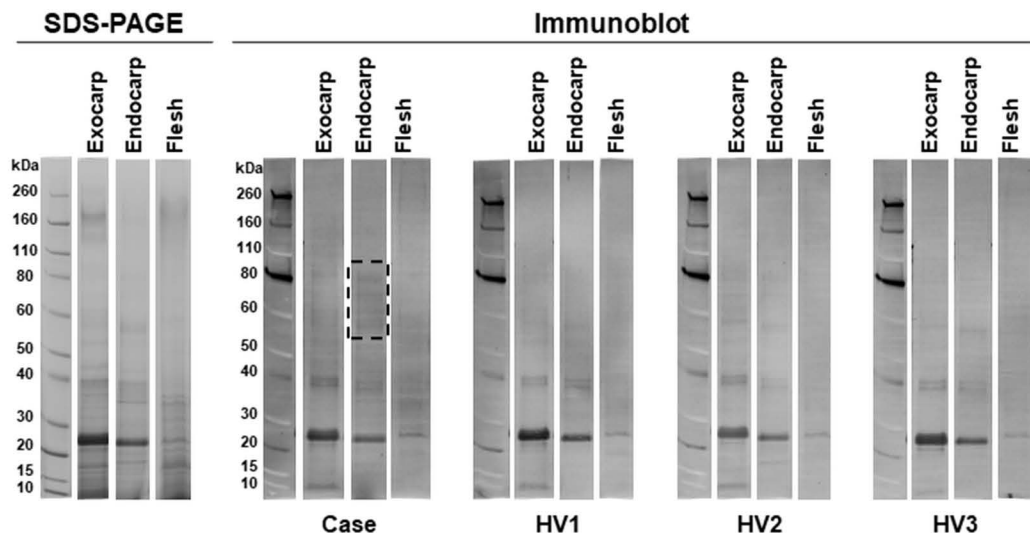
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Supplementary Fig. 1. Basophil activation test to (a) yuzu bath additives, (b) pectin, or (c) cashew nuts. Anti-IgE antibodies were used as positive controls. Basophils from the patient (case) upregulated CD203c when mixed with yuzu bath additives, pectin, or cashew nuts, whereas no upregulation was observed with basophils from a healthy volunteer (HV) when incubated with (d) yuzu bath additives, (e) pectin, or (f) cashew nuts. Summary of the percentage of activated CD203c^{high} basophils of the case or HV when mixed with (g) yuzu bath additives, (h) pectin, or (i) cashew nuts.



Supplementary Fig. 2. 1-D Western blot (WB) assay of control, exocarp, endocarp, and flesh of yuzu. The outer layer comprises the exocarp. Inside the exocarp, a whitish endocarp enfolds the flesh of the fruit. Case-specific IgE bound to a 50–80 kDa fragment of the yuzu endocarp (area within dotted line) compared with healthy volunteers (HV1, HV2, HV3). For the WB, 5% sera from the patient and healthy volunteers were used as the primary antibody, followed by horseradish peroxidase-conjugated anti-human IgE antibody (SeraCare Life Sciences, Inc., MA, USA).