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Letter to the Editor

Food-dependent exercise-induced anaphylaxis due to pickled Japanese apricot

Dear Editor,

Prunus mume, also known as Japanese apricot (JA), is an ornamental flower and fruit tree that belongs to the *Rosaceae* family. In Japanese cuisine, JA is used to make juices, an alcohol flavoring, pickles, and sauces. Some studies have described JA allergies,^{1–4} and the causative allergen remains incompletely understood. Herein, we present a case of food-dependent exercise-induced anaphylaxis (FDEIA) due to pickled Japanese apricot, *umeboshi*, and we examined the causative allergens.

A 41-year-old woman reported three episodes of anaphylaxis within the past 3 years. The first episode was characterized by itching of the scalp and shortness of breath in the morning. The second episode occurred after she had eaten sushi for dinner, and she experienced shortness of breath the next morning. It was unclear whether the patient had breakfast before or after these episodes. During the third episode, she experienced shortness of breath, facial edema, and low blood pressure (70/50 mmHg) 10 min after eating breakfast, which included rice and *umeboshi*.

Upon admission, the total serum immunoglobulin (Ig) E was 128 IU/ml. Immuno CAP specific IgE testing (Thermo Fischer Scientific, USA) results showed class 4 for Japanese cedar pollen, class 2 for cypress pollen, and class 1 for orchard grass and peach. Rice had class 0 results and the patient had eaten rice daily without any symptoms, therefore we excluded rice for the allergen. Skin-prick test results were positive for Japanese cedar, grass, ragweed, black pine, timothy, goldenrod, and mugwort pollens. We performed a skin-prick test to detect reactions to food that the patient consumed at dinner the night before and at breakfast on the day she experienced anaphylaxis. Food skin-prick tests were positive for peach, *umeboshi* (flesh and seed), Japanese apricot liquor (flesh and liquor), peach juice, pear, prune, strawberry, apple, Japanese pear, plum, cherry, kiwi fruit, and grape (Fig. 1). The patient developed oral itching in response to the skin-prick test.

Based on the fact that the patient had pollinosis, we suspected a pollen food allergy syndrome (PFAS). However, rPru p 1 (a Bet v1-related protein) and rPru p 4 (profilin), two allergens related to PFAS, produced a negative result in a cap-system fluorescence enzyme immunoassay (Thermo Fischer Scientific). rPru p 3, a subtype of the lipid transfer protein (LTP), also produced a negative result. The patient had not consumed any peach on the day she developed anaphylaxis; however, she ate rice and *umeboshi* for breakfast almost every day, and she habitually drank homemade JA juice and liquor. Because all three episodes occurred in the

morning, we suspected that the patient had a JA allergy. We performed an oral food challenge test with JA, but no reaction occurred after ingesting 24 g of *umeboshi* flesh. When we interviewed the patient in greater detail, she revealed that she frequently took a high dose of nonsteroidal anti-inflammatory drugs (NSAIDs) for menstrual pain or headaches.

Next, we performed a provocation test by combining *umeboshi* and NSAIDs to investigate the suspicion of a JA allergy enhanced by aspirin. The patient took 60 mg of loxoprofen an hour before ingesting JA. In this test, the patient developed itching in the oral mucosa and hands, conjunctival hyperemia, lachrymation, and sneezing within 30 min of ingesting 24 g (two pieces) of *umeboshi* flesh after taking loxoprofen. She experienced shortness of breath, hoarseness, facial edema, and low blood pressure (70/40 mmHg) within 40 min. We also performed an exercise provocation test. Here, the patient performed a stepping exercise after ingesting 12 g of *umeboshi*. After 10 min, she experienced frequent sneezing, nasal discharge, and itching of the eyes. With continued exercise, she experienced swelling of the throat. The patient was diagnosed with FDEIA due to JA, and we prescribed an auto-injector of epinephrine.

A serum sample was tested in an enzyme-linked immunosorbent assay (ELISA) with gibberellin-regulated protein (GRP) in peach, also known as peamaclein or Pru p 7 (Fig. 2a). We used *E. coli* product recombinant Pru p 7 purified using monoclonal antibody columns.⁵ The absorbance values of ELISA using the patient's serum were almost five times higher than that using normal control mix sera. In addition, the value of the patient's serum was significantly higher than that of normal mix ($p < 0.001$; $n = 3$ measurements). Therefore, the obtained ELISA result might show a positive reaction compared to normal control. Moreover, we have also performed inhibition ELISA assay by using JA protein extract. Briefly, JA protein was extracted by homogenizing frozen raw JA with commercial mixer. After homogenizing, the extract was filtered through four layers of gauze. ELISA plates were coated with peach rGRP overnight at 4 °C. After blocking and washing the wells, 1:50 dilutions of sera from the patient, with various concentrations of JA proteins (0.1 and 0.5 mg/ml; final concentrations), were co-incubated for 1 h at room temperature and subsequently placed in the wells. After a 1-h incubation at room temperature and 5 washes with PBST, a HRP-conjugated goat anti-human IgE antibody was added to the wells, followed by a 1-h incubation at 37 °C. After washing the wells 5 times with PBST, the bound secondary antibodies were detected through their reactions with a TMB peroxidase substrate. The reaction was stopped with 1 M phosphoric acid, and the absorbance at 450 nm was measured

Peer review under responsibility of Japanese Society of Allergology.

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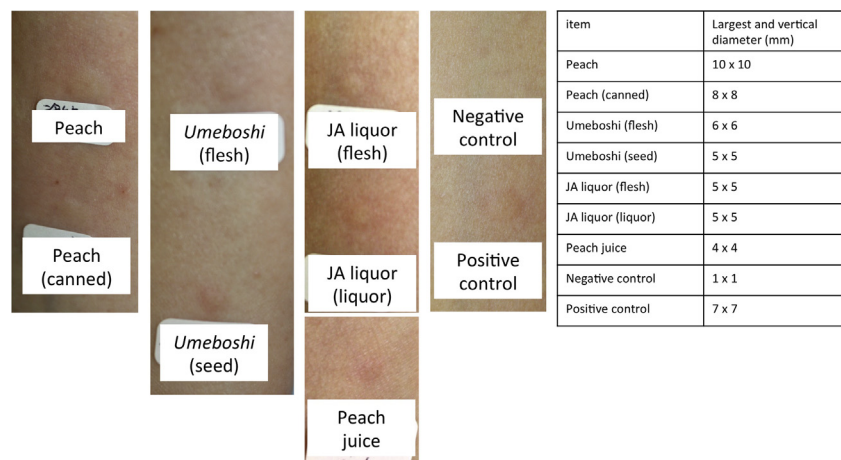


Fig. 1. Skin-prick test shows positive results for peach, *umeboshi* (flesh and seed), Japanese apricot liquor (flesh and liquor), and peach juice. The cutaneous reaction to the skin-prick test was considered positive, when the largest diameter of the wheal induced by the allergen was more than half the size of the wheal induced by histamine.

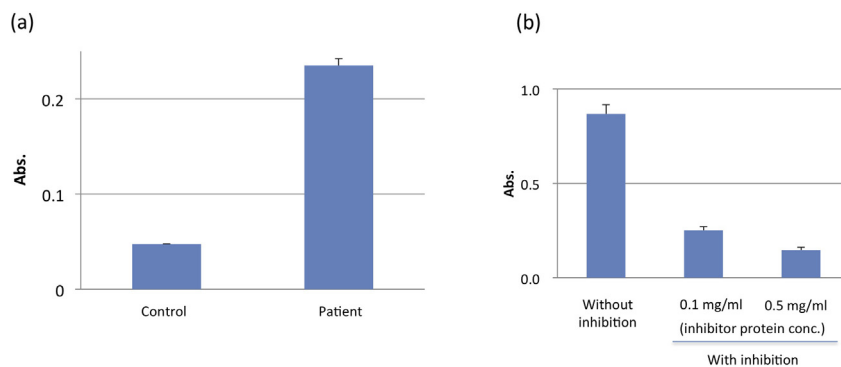


Fig. 2. ELISA results with patient's serum IgE. (a) Serum showed a positive reaction to gibberellin-regulated protein (GRP) from peach. (b) Inhibition assay shows that the reaction of serum IgE to peach GRP was inhibited selectively by adding Japanese apricot (JA) protein extract (The concentrations of the inhibitor: 0.1 and 0.5 mg/ml). Responses to different dilutions of JA protein extract indicate that the inhibition was concentration-dependent. Abs: absorbance measured in ELISA assays (means $\pm$ SD, $n = 3$).

using the plate reader. IgE binding to peach rGRP was dose-dependently inhibited by adding JA protein extract (Fig. 2b). This result indicated that JA contained GRP and it competed with peach GRP for binding to IgE. These findings suggested that the patient developed anaphylaxis after ingesting *umeboshi*, and the reaction was enhanced with loxoprofen administration. The diagnosis was FDEIA or/and food-dependent salicylate-induced anaphylaxis (FDSIA) in response to JA ingestion. The patient provided informed consent for this study and approved by our institutional review board.

GRP (peamaclein, Pru p 7) was first identified by Tuppo *et al.* as a new peach allergen, distinct from LTP (Pru p 3).^{6,7} Inomata *et al.* reported that GRP was the first known allergen to cause a JA allergy.¹ They also reported that six of seven patients with JA allergies developed allergic reactions when JA consumption was combined with physical exercise or aspirin intake.¹ They also identified the GRP of JA named Pru m 7.¹ Three other cases of JA allergy were described previously,^{2–4} and of those, two were associated with exercise or aspirin administration.^{3,4} In another study, Pru m 7 was the major allergen detected in 7 of 10 cases¹; in one case, a 50–60-kDa protein and a 45–97-kDa protein were detected.⁴ Inomata *et al.* indicated that food allergies caused by GRP typically induce severe allergic reactions, and we should be noted.⁸ It is difficult to acquire evidence of habitual or irregular NSAIDs use without a detailed interview. Care should be taken in recording the patient history, to ensure this diagnostic clue is not missed.

Conflict of interest

The authors have no conflict of interest to declare.

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Received 13 July 2018

Received in revised form 5 February 2019

Accepted 21 February 2019

Available online xxx