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Pollen food allergy syndrome to tomato in mountain cedar pollen hypersensitivity

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ABSTRACT

Background: Mountain cedar pollen is recognized as a major cause of seasonal hypersensitivity in the US. We describe here that a subgroup of these patients also suffer from pollen food allergy syndrome (PFAS).
Objective: We performed this study to determine the frequency of PFAS among patients with mountain cedar hypersensitivity.
Methods: We performed mail-out/telephone surveys of 800 mountain cedar-sensitive patients in Austin, TX. The subjects for this survey were selected by telephone screening, and skin and serologic testing. We performed immunoblot inhibition assay and mass spectrometry (MS) to identify the allergens that cause PFAS.
Results: Of the 28 patients with suspected food allergies, 15 had clinical manifestations of PFAS. Eleven of them had positive skin tests to tomato, six to banana, and one to apple. The subjects with PFAS have stronger cutaneous and in vitro reactivity to cedar pollen. The intensities of the tomato and banana reactivity were correlated with the cedar reactivity. The results of the ImmunoCAP inhibition experiments demonstrated a strong cross-reactivity between IgE antibodies to cedar pollen and fruits. This suggested that their primary sensitization was to cedar pollen, since absorption with cedar pollen extract strongly inhibited reactivity to each of the fruits, while the absorption with tomato extract did not significantly inhibit IgE binding to cedar extract. We determined that polygalacturonase 2 A (PG2 A) in tomato is the cause of PFAS.
Conclusion: This is the first report of a PFAS in patients with mountain cedar pollinosis. Sensitivity to tomato, banana, and apple should be considered in cedar-sensitive patients.

1. Introduction

Mountain cedar (*Juniperus ashei*, Cupressaceae) pollen is a major cause of seasonal hypersensitivity in the central USA. Patients with hypersensitivity to other pollen allergens have been found to have PFAS (Wagner et al., 2016), based on allergic reaction of their lips, mouth, and pharynx after eating native fruits and vegetables. PFAS is thought to occur when IgE anti-pollen allergen antibodies cross-react with the plant food allergens. Studies of the major tomato [*Solanum lycopersicum (Lycopersicon esculentum)*, Solanaceae)] allergens noted that all of the tomato-induced PFAS patients in Japan suffer from Japanese cedar (*Cryptomeria japonica,* Taxodiaceae) pollinosis (Kondo et al., 2002; Tokuda et al., 1999). Also, IgE antibodies that bind to Cry j 2, one of the major Japanese cedar allergens, cross-reacts with the tomato fruit allergen, PG2 A. PFAS has not been associated with mountain cedar pollinosis. However, since the mountain cedar allergens Jun a 1 (Midoro-Horiuti et al., 1999a, b), Jun a 2 (Yokoyama et al., 2000), and Jun a 3 (Midoro-Horiuti et al., 2000) have high homologies to pectate lyases (Marin-Rodriguez et al., 2002), PG2 A and pathogenesis related (PR)-5 protein (Midoro-Horiuti et al., 2001), respectively, common proteins among plants, we surmised that PFAS might be related to mountain cedar pollen hypersensitivity.

We tested a group of mountain cedar sensitized patients for PFAS to tomatoes, other fruits or vegetables, or other common allergenic food. We hypothesized that patients sensitized to mountain cedar pollen develop PFAS to tomatoes, because their IgE anti-cedar pollen antibodies cross-react with the allergens in tomato.

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2. Methods

2.1. Patient recruitment

Eight-hundred postcards were sent to mountain cedar pollen sensitive patients from Dr. van Bavel's Allergy Clinic, in Austin, TX, asking whether they had any symptoms of food allergy. Fifty of these patients replied and were screened by phone calls. Twenty-eight of these patients were interviewed in the allergy clinic. Each of these subjects were skin tested for mountain cedar pollen and a panel of food allergens. Sera were collected from the skin test positive patients and stored in −20 °C until the time of the further study. This project had been approved by the Institutional Review Board at the University of Texas Medical Branch (UTMB, #06-050). All subjects agreed to informed consent and participated in the study.

2.2. Native allergen preparation

A crude extract of mountain cedar pollen was prepared, as described previously (Midoro-Horiuti et al., 1999a). Briefly, mountain cedar pollen was purchased from Hollister-Stier (Spokane, WA). Pollen was extracted in 0.125 M ammonium bicarbonate (pH 8.0) containing 0.02% sodium azide and 50 μM 4-(2-aminoethyl)-benzenesulfonyl fluoride and the supernatant was collected after centrifugation. Protein was precipitated with 80% saturation with ammonium sulfate and the resulting precipitate was collected.

Jun a 1 was purified from mountain cedar crude extract using Con-A Sepharose 4B (GE Healthcare, Chicago, IL) chromatography (Midoro-Horiuti et al., 1999a). The purified Jun a 1 was dialyzed against 0.05 M Tris-HCl buffer, pH 7.8 or 0.5x PBS (0.15 M NaCl and 0.025 M KH_2PO_4-$KHPO_4$ at pH 7.1). The purity of Jun a 1 was established by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), reverse-phase HPLC and MS.

Jun a 3 was purified from mountain cedar pollen crude extract using HPLC C4 column, as described previously (Midoro-Horiuti et al., 2000).

Crude extract of tomato fruit was prepared, as described previously (Kondo et al., 2002), by extracting in 1 M NaCl from tomato pericarp and mixing with 75% saturation with ammonium sulfate. Banana and apple crude extracts were prepared as described for tomato crude extract.

2.3. ImmunoCAP assay

To measure the specific IgE in these patient sera, ImmunoCAP (ThermoFisher Scientific, Waltham, MA) assay was performed to mountain cedar, tomato, banana, and apple. Inhibition assays were performed using ImmunoCAP positive sera to tomato, banana, and apple. Protein concentration of crude extract was measured on the SDS-PAGE and Coomassie blue staining. Total protein concentration of crude extract of mountain cedar and tomato was used at 0.1 mg/ml. Each patient serum was incubated with inhibitor, crude extract of mountain cedar and tomato, at 4 °C overnight with gentle shaking. After incubation of inhibitors, the remaining serum IgE to mountain cedar, tomato, banana, or apple was measured by ImmunoCAP.

In order to analyze the cross-reactivity based on the common plant carbohydrate, we used 0.25 mg/ml pineapple stem bromelain (BRO, Sigma) to inhibit the IgE binding to mountain cedar and tomato crude extract (Afferni et al., 1999). The same concentration of ovalbumin (OVA) was used as a negative control.

2.4. SDS-PAGE and Western blotting

SDS-PAGE was performed on 15% acrylamide gels (Bio-Rad, Hercules, CA). Proteins in the gel were identified with Coomassie blue. Proteins were electrotransferred to nitrocellulose for Immunoblot and Immunoblot inhibition analysis. For Immunoblot inhibition, patient sera were preincubated at 4 °C overnight with cedar crude extract, or bovine serum albumin (BSA) as a control. Membranes were blocked with 10% fat-free milk in Tween-Tris buffered saline (TTBS), incubated with preincubated patient sera overnight, followed by biotinylated anti-human IgE (Vector laboratories, Burlingame, CA) for 4 h and peroxidase-streptoavidine (Zymed), and developed with enhanced chemiluminescence (ECL, ThermoFisher Scientific).

2.5. MS analysis

Tomato proteins which were inhibited by preincubation with cedar crude extract were analyzed by MALDI-MS [Perkin-Elmer Applied Biosystems (PE-ABI) Voyager instrument] at the Biomolecular Resource Facility at the University of Texas Medical Branch (Soman et al., 2000).

2.6. Sequence comparison of tomato pectate lyase and Jun a 1 from mountain cedar pollen

Tomato pectate lyases from GenBank and Jun a 1 from mountain cedar sequences, were compared. Tomato pectate lyases had about 50% identity to Jun a 1. IgE epitope regions of Jun a 1 (Midoro-Horiuti et al., 2003) had relatively higher sequence similarity to tomato pectate lyases, 30.7–62.5% identity and 46.2–76.9% homology.

3. Results

3.1. Clinical symptoms of study population

Twenty-eight patients were recruited to the study. Their symptoms included from lip swelling (n = 2) and itching, mouth itching (n = 4), mouth rash (n = 2), mouth sores (n = 2), swollen tongue (n = 1), lip itching (n = 1) during the consumption of fresh tomato, throat itching (n = 4), and throat swelling (n = 4).

3.2. Skin test results

The skin test results are shown in Table 1. Positive results were noted for tomato (n = 11), banana (n = 4), melon mix (n = 2), apple (n = 1), wheat (n = 7), peanuts (n = 3), pecan (n = 2), lima bean (n = 1), soy bean (n = 1), green bean (n = 1), fish mix (n = 5), shrimp (n = 3), lobster (n = 1), crab (n = 1) and milk (n = 2). Skin test-positive food allergies seen in individuals who self-reported the clinical symptoms were tomato (6/10, 60%), banana (2/5, 40%), melon mix (2/3, 67%), wheat (2/2, 100%), peanuts (2/4, 50%), pecan (1/2, 50%), lima bean (1/1, 100%), fish mix (1/3, 33%), lobster (0/1, 0%), crab (0/0, 0%), and milk (0/2, 0%). The confirmative oral food challenges have

Table 1
Skin test positive food allergies among mountain cedar pollen hypersensitivity (n = 28).

Group	Food	positive patients
Fruit	tomato	11
	banana	4
	melon mix	2
	apple	1
Grains	wheat	7
	peanuts	3
	pecan	2
Beans	lima bean	1
	soy bean	1
	green bean	1
Seafood	fish mix	5
	shrimp	3
	lobster	1
	crab	1
Dairy	milk	2

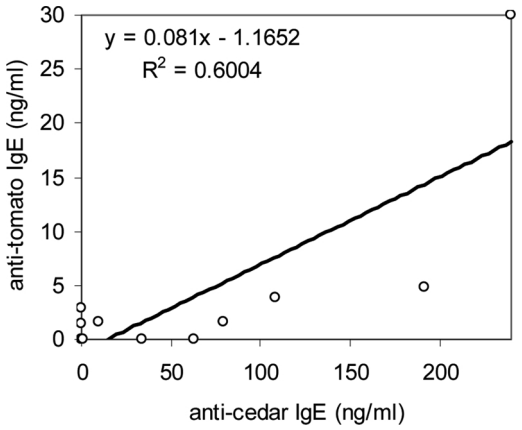

Fig. 1. Correlation between cedar specific IgE and tomato specific IgE in PFAS patients. Specific IgE concentration of the recruited patients to mountain cedar pollen and tomato are measured using ImmunoCAP among 28 patients. Specific IgE concentrations in their sera (ng/ml) are shown.

not yet been carried out.

3.3. ImmunoCAP and ImmunoCAP inhibition

Serological testing of skin test-positive patients was validated by ImmunoCAP analyses. Sera from eleven subjects had higher than 3 ng/ml (1.25 KU/L) IgE to mountain cedar. Seven of these reacted to tomato, three to banana, and one to apple. These sera were tested in an inhibition assay with specific allergens. There was a positive correlation between cedar specific IgE and tomato specific IgE as shown in Fig. 1.

To analyze the degree of cross-reactivity between cedar, tomato and banana crude extracts, we preincubated patient sera with each crude extract and performed ImmunoCAP. Fig. 2a shows the inhibition assay with cedar, tomato, and banana crude extracts. Preincubation with cedar extract inhibited 77.6 ± 23.9% of the IgE binding to cedar ImmunoCAP, 47.7 ± 13.7% to tomato ImmunoCAP and 40.4 ± 31.3% to banana ImmunoCAP. Pre-incubation with tomato extract inhibited 20.4 ± 29.0% of IgE binding to cedar and 66.0 ± 21.9% to tomato binding. Preincubation with banana extract inhibited 40.4 ± 31.3% to cedar and 72.4 ± 17.0% to banana binding.

To determine the cross-reactive allergen, we used Jun a 1, Jun a 3 and BRO preincubated sera before the ImmunoCAP assay. OVA was used as a negative control. Fig. 2b shows that the majority of anti-cedar IgE was against Jun a 1. Anti-tomato IgE was directed to Jun a 1, Jun a 3 and carbohydrate to a similar degree.

3.4. SDS-PAGE, immunoblot inhibition and MS

To determine which allergen cross-reacted, we preincubated patient sera with mountain cedar extract before Immunoblotting. BSA was used as a negative control. Fig. 3 shows the electrophoresis pattern of tomato extract and Immunoblot inhibition assay. Preincubation with mountain cedar extract reduced the IgE binding to the 34 kD band in tomato extract. MS analysis identified this band as PG-2 A from tomato (GenBank: CAA32235).

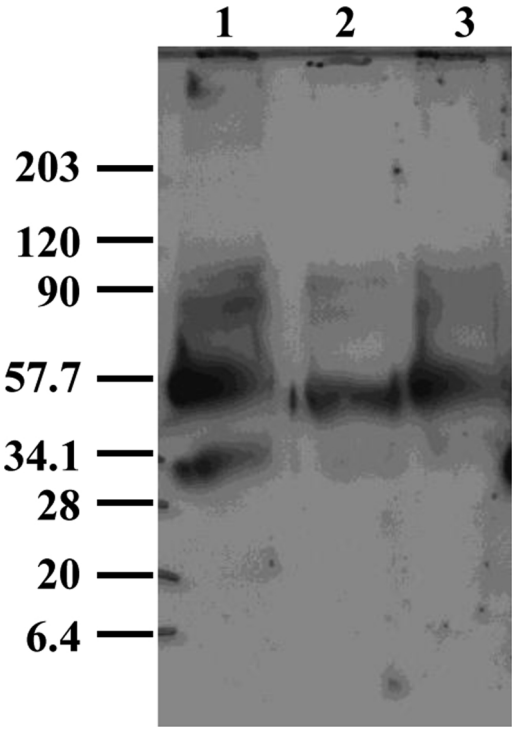

Fig. 3. Immunoblot inhibition assay. Tomato crude extract was electrophoresed and transferred to the nitrocellulose membrane. The membrane was incubated with patient serum with (Lane 2 and 3) and without (Lane 1) preincubation with cedar crude extract. Bound IgE was detected with biotinylated anti-IgE and ECL.

4. Discussion

We previously identified and cloned mountain cedar pollen allergens, Jun a 1 (Midoro-Horiuti et al., 1999a) and Jun a 3 (Midoro-Horiuti et al., 2000), and others have found Jun a 2 (Yokoyama et al., 2000). All of these allergens have high homology to allergens in fruits. We were interested in the PFAS among mountain cedar pollen hypersensitivity patients. The best studied PFAS is an apple allergy among birch pollen hypersensitivity. Up to 60% of the birch pollen hypersensitivity patients suffer from apple allergy (Wagner et al., 2016).

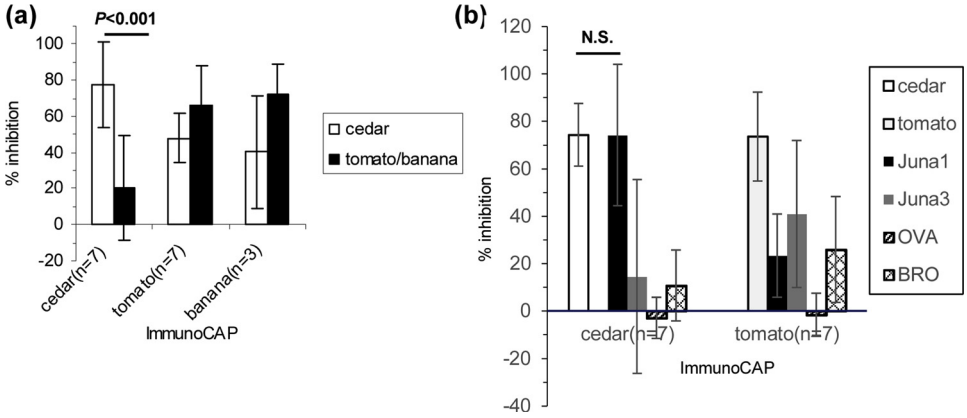

Fig. 2. ImmunoCAP inhibition to cedar, tomato, and banana. Direct and indirect inhibition to cedar, tomato, and banana were analyzed after serum preincubation with their crude extract. Individual data and mean ± SD were shown with bars. (a) $*p < 0.001$ as indicated. (b) OVA: negative control with ovalbumin preincubation, BRO: carbohydrate control with bromelain preincubation, N.S.: not significant.

Among patients with Japanese cedar pollen hypersensitivity, about 1% of tomato PFAS patients are reported (Kondo et al., 2002). Since about 30% of the whole population in Japan suffer from Japanese cedar pollen hypersensitivity, tomato PFAS could be a substantial problem (Ozasa et al., 1999). The prevalence of tomato allergy is estimated between 1.5–16% among food-allergic populations and 39.2% among grass pollen allergies (Westphal et al., 2003). Others recently report on peach allergy in cypress pollen hypersensitive persons due to gibberellin, Pru p 7 (Klingebiel et al., 2019; Senechal et al., 2019). The results of our ImmunoCAP inhibition assay with crude extract showed that most of IgE reactivity to both cedar and tomato was inhibited by preincubation with cedar extract, while preincubation with tomato only inhibited the IgE reactivity to tomato and banana (Fig. 3). These results indicate that the IgE is directed to cedar pollen and cross-reacts with tomato, banana, and apple. A recent study showed that Japanese cedar pollen-based immunotherapy decreased the tomato-specific basophil activation (Inuo et al., 2015), which supports our results.

There are seven tomato allergens and four potential others have been reported, Sola l 1: profilin (Willerroider et al., 2003), Sola l 2: β-fructofuranosidase (Westphal et al., 2003), Sola l 3: lipid-transfer protein (LTP), PG2 A (Kondo et al., 2001), Sola l 4: Bet v 1 homologous PR-10 (Wangorsch et al., 2015), Sola l 5: cyclophilin (WHO/IUIS Allergen Nomenclature Sub-Committee), Sola l 6: non-specific LTP type 2 (nsLTP2, WHO/IUIS Allergen Nomenclature Sub-Committee), Sola l 7: nsLTP1 (WHO/IUIS Allergen Nomenclature Sub-Committee), superoxide dismutase (SOD) (Kondo et al., 2001), pectinesterase (PE) (Kondo et al., 2001), PR-protein P23 (Kondo et al., 2001) and gibberellin. Among these tomato allergens, the majority of patient serum IgE was against profilin Sola l l, and Sola l 1-silencing transgenic tomato has reduced allergenicity (Le et al., 2006; Westphal et al., 2004; Willerroider et al., 2003). In order to determine which allergen causes tomato PFAS among mountain cedar pollen hypersensitivity patients, we performed immunoblot inhibition assay with patient sera. Fig. 3 shows the inhibition by mountain cedar pollen crude extract to IgE binding to tomato proteins. The 34 kD protein in the tomato extract was identified as PG2 A using MS analyses. PG2 A has high sequence homology to group 2 allergens of cedars, Jun a 2, Cha o 2 and Cry j 2 (2). This result indicated that the causative allergens of tomato PFAS among mountain cedar pollen hypersensitivity are Jun a 2 and PG2 A, similar to those of PFAS in Japanese cedar pollen hypersensitivity.

In this study, we used commercially available skin test solutions and ImmunoCAP inhibition assays. In some cases of food allergies, the prick-to-prick test is recommended, since there is a possibility that conformationally fragile allergens are only available in fresh foods. Though we could detect food sensitivities using the commercially available standard skin test solutions in this study, the prick-to-prick test may be required for the further investigations.

Skin test positivity among the self-reported food allergies in this study were higher than usual food allergy. This may be because PFAS patients have symptoms immediately after the food intake, compared to class I food allergy, which induces symptoms after more than a few minutes, or hours later.

In conclusion, this is the first report of PFAS in mountain cedar pollinosis patients. Sensitivity to tomato, banana, and apple should also be considered in cedar-sensitive patients.

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