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Letter to the Editor

Food-induced anaphylaxis in two patients who were using soap containing foodstuffs

Dear Editor,

Food allergies are considered to occur following gastrointestinal mucosa-mediated sensitization. However, some recent reports have suggested that food allergen sensitization can also occur through the skin.^{1,2} Food protein derivatives are widely used in various products, such as cosmetics and soaps. Here, we report two cases of food-induced anaphylaxis in patients who were using soap containing foodstuffs.

Patient no. 1 had washed her face using soap containing corn (Let The Good Times Roll; Lush) daily for about 3 months. At that time, she did not develop any symptoms after using the soap. However, when she started using the soap again (to wash her face) after an approximately 9-month period of non-use, facial redness and swelling, conjunctival congestion, pharyngeal discomfort, and erythema of the trunk and upper limbs developed within 30 min. The patient visited a hospital and was treated with intravenous and oral steroids, which relieved her symptoms. Twenty days later, she ate a snack, which contained an ingredient derived from corn, and labial swelling occurred. We suspected a corn allergy and performed prick tests with the soap, all ingredients of the soap, and a commercially available corn extract (Torii, Tokyo, Japan). Positive reactions to the soap (0.1% aq. and 0.01% aq.), corn-based ingredient (0.01% aq.), and corn extract (Torii) were detected during the prick tests (Table 1). Furthermore, the patient's serum levels of specific IgE against corn, foxtail millet, Japanese millet, and proso millet were elevated (Table 1). Immunoblotting (Supplementary Fig. 1) and subsequent mass spectrometry (Supplementary Table 1) were performed as previously reported (Supplementary Methods).³ The results indicated that there were several possible causative allergen components, that had not been reported as corn allergens. As the patient had never suffered any symptoms associated with the consumption of corn until she started using the soap, it was speculated that epicutaneous sensitization might have caused her corn allergy. The patient had never eaten millet and its related food. It was considered that cross-reactions between corn and foxtail millet, Japanese millet, and/or proso millet might have occurred. At one year after the patient had stopped using the soap, her serum levels of specific IgE against corn and millet had decreased to a quarter of their peak levels. At two years after the patient had stopped using the soap, no specific IgE against corn or millet were detected in her serum. However, when the abovementioned prick tests were repeated at one and two years after the patient had stopped using the soap, skin reactions of equal severity to those seen in the

original tests were observed. There has been no recurrence of the patient's allergic symptoms since she started avoiding foods containing corn.

Patient no. 2 had washed her whole body using soap containing oats and almonds (A-DERMA washing bar; Pola Pharma) daily for about 6 years. Two years after she started using the soap, wheals began to appear on her hands, which had been affected by eczematous lesions. Four years later, she developed wheals on her whole body, pharyngeal discomfort, and diarrhea after consuming food containing wheat and nuts, such as cakes and cookies. We suspected a food allergy and performed prick tests of the soap, a commercially available wheat extract (Torii), and nuts, as shown in Table 1. The prick tests showed positive reactions to the soap (0.1% aq.), wheat extract (Torii), and several kinds of nuts (as is) (Table 1). In three healthy controls, the prick tests showed negative reactions to the soap (0.1% aq.). The patient's serum levels of specific IgE against oats, wheat, or several kinds of nuts were elevated (Table 1). Anti-wheat IgE had not been detected in the patient's serum before she started using the soap; therefore, epicutaneous sensitization induced by the soap might have led to the development of a wheat allergy. The patient had never eaten the food including oats. It was speculated that cross-reactions between oat and wheat, or among various kinds of nuts might have occurred, although the detailed analysis of cross reactions was not performed. At half a year after the patient had stopped using the soap, her serum levels of specific IgE against oats, wheat, and nuts had decreased to a half of their peak levels. The patient subsequently stopped using the soap and avoided wheat and nuts, and her symptoms did not recur. However, when the abovementioned prick tests were repeated at half a year after the patient had stopped using the soap, skin reactions of equal severity to those seen in the original tests were observed. Furthermore, we performed open application tests and prick tests with all ingredient of the soap at eight months after stopping the soap use. The open application tests showed negative reactions to all ingredient of the soap, however, prick tests showed positive reaction to only oats (0.01%) (Table 1). The results suggest that the patient was percutaneously sensitized to oats in the soap. It was unclear whether the process of sensitization to nuts might be associated with the soap use or not.

In both cases, a food allergy developed following the appearance of soap-induced contact urticaria, suggesting that epicutaneous sensitization might be involved in the onset of some food allergies. About 2000 Japanese adults who used a facial soap (Chanoshizuku[®]) containing hydrolyzed wheat proteins developed allergic symptoms after consuming wheat.^{3,4} However, no cases of food

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Table 1
Patients' characteristics and test results.

Patient no.	1	2
Age/Sex	42/female	40/female
Other allergic diseases	Atopic dermatitis Asthma	Atopic dermatitis Pollinosis
Past history	None	Endometriosis
Serum total IgE levels (IU/ml)	59	3894
(Reference range: 0–380)		
Serum allergen-specific IgE levels (UA/ml)	IgE against	IgE against
(Reference range: 0.00–0.34) [†]	- Maize: 2.12	- Oats: 954.00
	- Foxtail millet: 1.71	- Wheat: 93.20
	- Japanese millet: 2.29	- Gluten: 80.20
	- Proso millet: 3.00	- Gliadins: 10.40
		- Rye: 31.00
		- Barley: 15.30
		- Almonds: 35.60
		- Brazil nuts: 33.50
		- Cashew nuts: 22.90
Prick test results [‡] : Score, Wheal diameter (mm × mm)	Histamine: 4 × 4 Saline: 0 × 0 Soap containing corn (0.01%): 2+, 2 × 2 Soap containing corn (0.1%): 3+, 4 × 3 Glycerin (as is) [§] : –, 0 × 0 Talc (10%) [§] : –, 0 × 0 Crocin (10%) [§] : –, 0 × 0 Cinnamon (10%) [§] : –, 0 × 0 Corn extracts (Torii): 4+, 5 × 11	Histamine: 7 × 7 Saline: 1 × 1 Soap containing oats and almonds (0.01%): 2+, 7 × 4 Wheat extracts (Torii): 2+, 5 × 5 Almonds: 4+, 9 × 6 Cashew nuts: 2+, 4 × 3 Hazelnuts: 2+, 5 × 3 Macadamia nuts: 2+, 6 × 4 Histamine: 5 × 5 Saline: 0 × 0 Oats (0.01%) [§] : 4+, 10 × 8 Almond oil (as is) [§] : –, 0 × 0 PEG-45 Palm Kernel Glycerides (1%) [§] : –, 0 × 0 Other mixed ingredients (10%) [§] : –, 0 × 0

[†] ImmunoCAP pollen allergens, Thermo Scientific.[‡] Evaluation of prick test results was performed as previously reported.^{12,13} The allergen wheal of similar size as that of histamine was given a relative size of 3+, if double the size of histamine 4+, and if half the size of histamine 2+. A positive result was defined as ≥2+.[§] Soap ingredients.[¶] Other mixed ingredients contain cetareth-6, cetaryl alcohol, citric acid, disodium lauryl sulfosuccinate, maltodextrin, microcrystalline wax, paraffin, polyethylene, sodium cocoyl isethionate, stearic acid, titanium dioxide, and water.

allergies that arose following epicutaneous sensitization to soap containing foods other than hydrolyzed wheat proteins have been reported.⁵ Substances with molecular weights of ≤500 can pass through healthy skin. Epicutaneous sensitization to food proteins requires macromolecular allergens to invade the skin and be taken up by antigen-presenting cells in the skin, e.g., Langerhans cells. Soap might impair skin barrier function by removing sebum, and thereby, facilitate percutaneous absorption of food allergens.

Both patients had suffered from atopic dermatitis and developed symptoms, such as wheals on their lesional skin, after using soap containing foodstuffs. Sano *et al.* have reported two cases of atopic dermatitis, who had contact urticaria following frequent contact of fish on their hands with eczematous lesions.¹ Furthermore, Inomata *et al.* reported that most patients who were thought to have been sensitized to food allergens via the skin had suffered from atopic dermatitis.² In the lesional skin of atopic dermatitis, skin barrier function is reduced through several mechanisms, including decrease of filaggrin⁶ or ceramide⁷ levels following Th2-type inflammation. Furthermore, Kubo *et al.* reported that in mice with reduced skin barrier function the dendrites of Langerhans cells are elongated and pass through the surrounding tight junctions and into the corneal layer.⁸ A similar phenomenon is observed within the lesions of atopic dermatitis patients, but not at non-lesional sites.⁹ We previously demonstrated that thymic stromal lymphopoietin (TSLP) expression is increased in the lesion of atopic dermatitis.¹⁰ Ebner *et al.* showed that TSLP greatly increases the numbers of migratory Langerhans cells that induce proallergic T cells.¹¹ Therefore, using soap containing food proteins might result in epicutaneous sensitization to food allergens, especially in patients with atopic dermatitis. Based on the present cases, clinicians should keep in mind that sensitization to food allergens

can occur through the skin in individuals that use soap containing foodstuffs.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.alit.2018.02.013>.

Conflict of interest

The authors have no conflict of interest to declare.

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Supplementary Methods

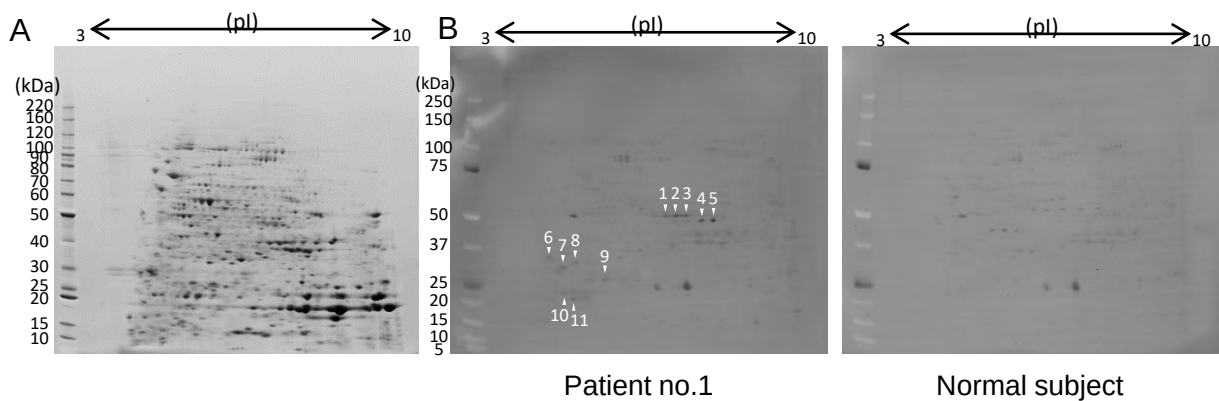
2D-PAGE and IgE immunoblotting

Proteins of corn were extracted with 30mM Tris-HCl (pH8.5), 2M Thio Urea, 7M Urea, and 4%(w/v) CHAPS. A total of 50 µg of protein lysate was separated using 2D gel electrophoresis (7 cm Immobiline DryStrip (IPG) pH 3–10 NL (GE Healthcare) and Novex NuPAGE 4–12% Bis-Tris gel with NuPAGE MOPS SDS Running Buffer (Life Technologies)) and transferred to PVDF membranes, Immobilon-FL PVDF (Millipore). Membranes were blocked with 5% skim milk/PBS-T for 1 hour at room temperature followed by incubating with a total of 5% serum diluted in 5% skim milk/PBS-T for 1 hour at room temperature. The membranes were incubated with 0.2 µg/ml anti-human IgE-HRP conjugate (KPL) in 5% skim milk/PBS-T for 1 hour at room temperature and chemiluminescence reaction was developed by ECL Plus Western Blotting Substrate (Thermo Fisher Scientific Inc.). The fluorescent image was captured using Typhoon FLA 9500 (GE Healthcare).

Supplementary Table 1. Results of mass spectrometry for the causative allergen components.[†]

	pI	MW	Coverage (%)	Accession #	Name
1	6.08	47.3	46.3	NP_001148829.1	elongation factor 1-gamma 3 [Zea mays]
2	6.08	47.3	54.4	NP_001148829.1	elongation factor 1-gamma 3 [Zea mays]
3	6.08	47.3	41.3	NP_001148829.1	elongation factor 1-gamma 3 [Zea mays]
4	6.73	43	43.1	XP_020398166.1	ERBB-3 BINDING PROTEIN 1-like [Zea mays]
5	6.73	43	40.6	XP_020398166.1	ERBB-3 BINDING PROTEIN 1-like [Zea mays]
6	4.56	36.1	36.3	AQK53536.1	GrpE protein-like protein [Zea mays]
7	4.76	29.7	83.5	sp P49106.1 14331_MAIZE	RecName: Full=14-3-3-like protein GF14-6
7?	4.82	28.9	79.3	ONM04671.1	14-3-3-like protein GF14 nu [Zea mays]
8	5.04	32.4	56.8	XP_008677270.1	alpha-soluble NSF attachment protein isoform X1 [Zea mays]
9	5.52	27	65.2	sp P12863.3 TPIS_MAIZE	RecName: Full=Triosephosphate isomerase, cytosolic; Short=TIM; Short=Triose-phosphate isomerase
10	5.53	25	18.8	ONM04544.1	Ribonuclease 1 [Zea mays]
11	5.14	22.5	51.2	NP_001130744.1	Ras protein RIC1 [Zea mays]

[†] Mass spectrometry was performed following IgE immunoblotting and the protein names were identified according to NCBI (<https://www.ncbi.nlm.nih.gov/>).



Supplementary Fig. 1. Results of two dimensional polyacrylamide gel electrophoresis (2D-PAGE) (A) and IgE immunoblotting (B) of corn. (A) Proteins were extracted with urea and were fractionated by 2D-PAGE. (B) Sera from the patient (left figure) or normal subject (right figure) as control were used. Several protein spots, that were strongly combined with IgE, were marked (left figure). The spots were not detected in IgE immunoblotting using sera from another normal subject (data not shown).