



Original article

Food allergy preceded by contact urticaria due to the same food: Involvement of epicutaneous sensitization in food allergy



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AD atopic dermatitis

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ABSTRACT

Background: There have recently been reports suggesting that sensitization to food allergens may occur outside the intestinal tract, especially through the skin. To clarify the role of epicutaneous sensitization in food allergy, we investigated the clinical characteristics of adult patients with food allergies preceded by contact urticaria due to the same foods.

Methods: We investigated clinical characteristics of 15 patients (20–51 years of age; 5 men and 10 women), who had food allergies preceded by contact urticaria.

Results: Fourteen patients were contact urticaria due to the causative foods during occupationally cooking, whereas 1 patient during face pack. In the occupational group, causative foods included rice, wheat, fruits, vegetables, fish, shrimp and cuttlefish; in the fresh cucumber paste case the cause was cucumber. In the 15 patients, the causative foods were fresh, not processed, and were tolerated by most (9/15, 60%) after heating. Regarding to symptoms after ingestion of the causative foods, the most frequently induced symptoms was oral symptoms (14/15, 93.3%), followed by urticaria (4/15, 26.7%), abdominal symptoms (3/15, 20%). The duration between the start of jobs or face pack, and the onset of contact urticaria was from 1 month to 19 years (mean, 8.7 years). The duration between the onset of contact urticaria and the onset of food allergy was from a few weeks to 6 years (mean, 11 months). One sushi cook experienced severe anaphylactic shock after ingestion of fish. In the occupational group, 13 of 15 patients (86.7%) had atopic dermatitis or hand eczema, indicating that the impaired skin barrier might be a risk for food allergies induced by epicutaneous sensitization.

Conclusions: Epicutaneous sensitization of foods could induce food allergy under occupational cooking and skin-care treatment with foods in adults.

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Introduction

Food allergy has been classically thought to occur due to sensitization of food through the gastrointestinal tract. However, it has been hypothesized that sensitization to food antigen can occur even if the primary exposure to food allergens is through non-oral routes. This is largely due to the observation that some children have adverse reactions upon their first ingestion of allergens, suggesting that oral ingestion may not be the only means of sensitizing to an allergen.¹ One epidemiologic study also found that children with a positive food challenge to peanuts were more likely to have used creams containing peanut oil, raising the possibility that

skin exposure may be inducing sensitization.² Indeed, mice have been successfully sensitized to food allergens in an adjuvant-independent manner through epicutaneous routes.^{3–5} Furthermore, nearly 2000 Japanese adults, who used a special facial soap (Chanoshizuku®) containing hydrolyzed wheat proteins (HWPs) developed allergic reactions after ingestion of wheat, indicating that epicutaneous sensitization to HWP in the soap might have induced wheat allergy.⁶ These patients had shown no symptoms upon ingestion of wheat before use of the soap, suggesting that epicutaneous sensitization can occur even in individuals with established oral tolerance. According to the reports of the Special Committee for the Safety of Protein Hydrolysates in Cosmetics of the Japanese Society of Allergy (<http://jsall-web.sharepoint.com/Pages/report2.aspx>), most of these patients (60%) experienced contact urticaria due to HWP soap before the onset of food allergy due to wheat.

In the present study, we investigated the clinical characteristics of 15 adult patients in whom food allergy was preceded by contact

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urticaria due to the same food, suggesting that epicutaneous sensitization may have involved the allergy.

Methods

Patients

Outpatients, who had previously experienced localized immediate allergic reactions to foods, and thereafter developed allergic responses by ingesting them, were recruited into this study. Patients were all seen at the Department of Dermatology of Yokohama City University Hospital in the 7-year period between January 2004 and December 2011. Two of the patients, sensitized to fish and rice, were described previously.^{7,8} Patients with positive results for specific IgE measurements, SPTs, and/or challenge tests with the suspected foods were diagnosed with “food allergies following epicutaneous sensitization”. After providing informed consent, participating patients underwent skin and blood tests to diagnose food allergies. This study was approved by our institutional review board.

Laboratory tests

Serum total IgE and specific IgE levels (ImmunoCAP; Phadia, Uppsala, Sweden) for relevant foods were measured. The cutoff value of the assay was 0.7 kUA/l as class 2.

Skin prick test

Patients were subjected to diagnostic skin prick tests (SPTs) using commercial extracts, such as wheat and rice (Torii, Tokyo, Japan) according to standard procedures.⁹ In addition, fresh foods and

cooked foods that were suspected of inducing allergic reactions were also tested according to the prick-prick technique.¹⁰ Histamine dihydrochloride at 10 mg/ml and phosphate-buffered saline served as positive and negative controls, respectively. The elicited response was considered positive when the average wheal diameter induced by the allergen extract was $\geq 50\%$ of the positive control.⁹ Prick-prick tests with all foods were also carried out on 5 control subjects.

Results

Clinical characteristics of patients

Fifteen patients (mean age, 31.1 years; range, 20–51 years; 5 men and 10 women; $n = 15$) were diagnosed with food allergies following epicutaneous sensitization to foods (Table 1).

Epicutaneous exposure to food proteins in contact urticaria occurred as follows: cooks ($n = 9$, 60.0%) and housekeepers ($n = 5$, 33.3%) exposed to food as ingredients; an individual using foods to care for their skin, e.g., fresh cucumber paste face pack ($n = 1$, 0.7%) (Fig. 1). The face pack was applied after the skin was cleansed and scrubbed. These results indicated that the opportunity for contact urticaria due to foods could be divided into two groups: an occupational group, in which patients could be sensitized to foods via their skin during cooking and a fresh cucumber paste case, which could be sensitized to foods via its skin during skin-care treatments. (see Table 2).

The causative foods of allergic symptoms

The foods that induced symptoms after ingestion included rice, wheat, fruits, vegetables, fish, shrimp, and cuttlefish in occupational

Table 1
Clinical characteristics in patients of the occupational group and a fresh cucumber paste case.

Case No.	Age/sex	Opportunity for contact urticaria	Causative foods of food allergies	Duration		Symptoms after ingestion					Tolerability after heating foods	Other diseases
				Between the start of jobs or face pack, and the onset of CU	Between the onset of CU and FA	OS	UR/AE		LT	AS	CO	
							UR	AE				
1	20 F	Cook (Sushi)	Fish (horse mackerel, mackerel, salmon, amberjack, sole, conger)	1m	11m	+	+	–	+	+	–	AD, AR
2	26 F	Cook (Sushi)	Fish (salmon, horse mackerel, sardine, scallop)	1y	1y	+	+	–	+	+	–	AD
3	30 M	Cook	Lettuce, chicory	1y	1m	+	–	–	–	–	Unknown	None
4	35 M	Cook (Italian)	Wheat flour	9y	2m	+	–	–	–	–	+	AD
			Rice	14y	A few weeks	+	–	–	–	–	+	
			Lentils	19y	A few weeks	+	–	–	–	–	+	
5	22 F	Cook	Broccoli	2y	A few weeks	–	+	–	–	+	–	AD, AR
6	24 M	Cook	Fruits (orange, pineapple, kiwi)	5y	6m	+	–	–	–	–	+	HE
			Shrimp	5y	6m	+	–	–	–	–	–	
			Cuttlefish	5y	6m	+	–	–	–	–	–	
7	30 M	Cook	Vegetables (carrots, tomatoes)	5y	0m	+	–	–	–	–	+	AD, PO
8	30 M	Cook	Wheat flour	7y	9m	+	+	–	–	–	+	AD
9	39 F	Baker	Wheat flour	2y	6y	+	–	–	–	–	+	None
10	51 F	Housekeeper	Rice bran	3y	A few weeks	+	–	–	–	–	+	PO
11	33 F	Housekeeper	Vegetables (spinach, tomatoes, melons)	5y	A few weeks	+	–	–	–	–	+	HE, BA, PO
12	41 F	Housekeeper	Shrimp	10y	A few weeks	+	–	–	–	–	–	AD
13	40 F	Housekeeper	Grapes, cucumber	9y	A few weeks	+	–	–	–	–	+	AD, AR
14	44 F	Housekeeper	Carrots	7y	2y	+	–	–	–	–	+	AD, FA (wheat)
15	32 F	Face pack using fresh cucumber paste	Cucumber	5y	1y	+	–	–	–	–	Unknown	AD, PO

CU, contact urticaria; FA, food allergy; OS, oral symptoms; UR, urticaria; AE, Angioedema; LT, laryngeal tightness; AS, abdominal symptoms; CO, loss of consciousness; AD, atopic dermatitis; AR, allergic rhinitis; HE, hand eczema; FA, food allergy.

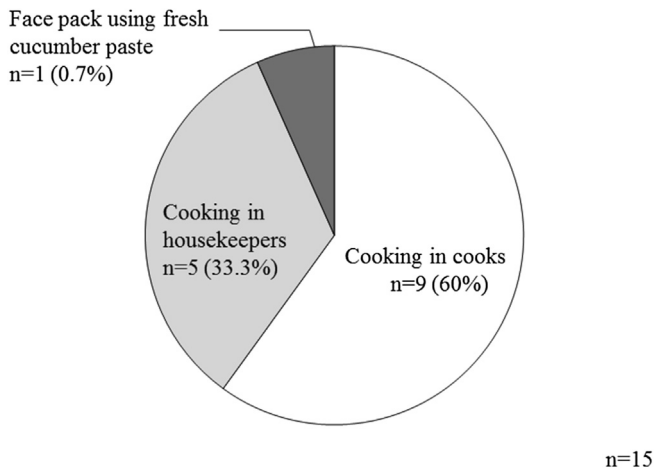


Fig. 1. The opportunity for contact urticaria to foods. Epicutaneous exposure to food proteins in contact urticaria occurred as follows: cooks ($n = 9$, 60.0%) and housekeepers ($n = 5$, 33.3%) exposed to food as ingredients; an individual using foods to care for their skin, e.g., fresh cucumber paste face pack ($n = 1$, 6.7%), indicating that the opportunity for contact urticaria to foods could be divided into two groups of an occupational group and a fresh cucumber paste case.

group; cucumber was the causative food in the fresh cucumber paste case (Table 1, Fig. 2). Vegetables were the most frequent causative foods in cooks and housekeepers.

In all other patients, the causative foods were fresh and not processed (Table 1). In addition, in the occupational group, patients with allergies to grains (such as rice and wheat) and vegetables (such as carrots, spinach and broccoli) could eat these foods cooked, for example, steamed rice, bread, or boiled vegetables. Three patients sensitized to wheat flour developed

allergic symptoms after tasting pasta and breads, which could not be fully boiled or baked. Meanwhile, the patients sensitized to raw fish developed symptoms after ingestion of cooked fish, such as conger and flounder.

The characters of the preceding contact urticaria

The length of time between when subjects started jobs or using the face pack and the onset of contact urticaria was from 1 month to 19 years (mean 8.7 years) (Table 1). The duration between the onset of contact urticaria and the onset of food allergy was from a few weeks to 6 years (mean 11 months). Urticaria appeared on the area exposed to the causative foods within approximately 30 min after the contact of causative foods. In all cases of the occupational group, contact urticaria occurred on the hands and/or arms, whereas it was induced on the face in the case of fresh cucumber paste. In one case (Case 3), contact urticaria was accompanied with generalized urticaria and dyspnea.

Clinical symptoms after ingestion of foods

In almost all patients (14/15, 93.3%), the main symptoms after ingestion were oral, including itching and swelling in the oral cavity and pharynx (Fig. 3). In the occupational group, all housekeepers developed relatively mild oral symptoms after ingestion of the causative foods, whereas cooks experienced more severe reactions, accompanied with skin symptoms, such as urticaria (5/9, 55.6%), respiratory symptoms (2/9, 22.2%), abdominal symptoms (3/9, 33.3%) and loss of consciousness (1/9, 11.1%). In particular, sushi cooks who became sensitized to fish experienced severe anaphylactic reactions after ingestion of fish. In the skin-care group, itching and swelling in the oral cavity was also induced by ingestion of fresh cucumber in the patient sensitized by cucumber.

Table 2
Results of allergy tests in the occupational group and the fresh cucumber paste case.

Groups	Case No.	Causative foods	Results of allergic tests			
			Serum specific IgE (ImmunoCAP [class])	Skin prick tests with raw foods	Challenge tests	Serum total IgE (IU/ml)
The occupational group	Cooks	1 Fish (horse mackerel, mackerel, salmon, amberjack, sole, conger)	Horse mackerel 3, salmon 3, mackerel ND, Amberjack: ND, sole ND, conger ND	All kind of fish +	Conger: +, laryngeal tightness, swelling of lips, abdominal pain	753
		2 Fish (salmon, horse mackerel, sardine), scallop	Salomon 1, horse mackerel 1, sardine 1, scallop 0	+	Salmon: +, oral tingling and swelling	186
		3 Vegetables (lettuce, chicory)	ND	+	+	1587
		4 Wheat flour	Wheat 4, gluten 3	+	Oral tingling	466
		Rice	2	+	Oral tingling, throat tightness, dyspnea	
		Beans (lentils)	ND	+	Oral tingling	
		Mushroom	ND	+	Oral tingling	
		5 Vegetables (broccoli)	ND	+	ND	183
		6 Fruits (orange, pineapple, kiwi)	ND	+	ND	ND
	House-keepers	Shrimp	ND	+	ND	
		Cuttlefish	ND	+	ND	
		7 Vegetables (carrots, tomatoes)	Carrots 4, tomatoes 3	Carrots+, tomatoes+	ND	1371
		8 Wheat flour	4	+	ND	14,244
		9 Wheat flour	Wheat 0, gluten 0, ω -5 gliadin 0	+	ND	8
		10 Rice bran	Rice 3	+	ND	652
		11 Vegetables (spinach, tomatoes)	Spinach 2, tomatoes 0	+(boiled-)	ND	1033
The fresh cucumber paste case	15	Fruits (melon)	1	+	ND	
		Shrimp	2	+	ND	22
		12 Vegetables (cucumber)	ND	+	ND	1401
		Fruits (grapes)	ND	+	ND	
		13 Vegetables (carrots)	3	+	ND	468
		Cucumber	ND	+	ND	48

ND, not floss.

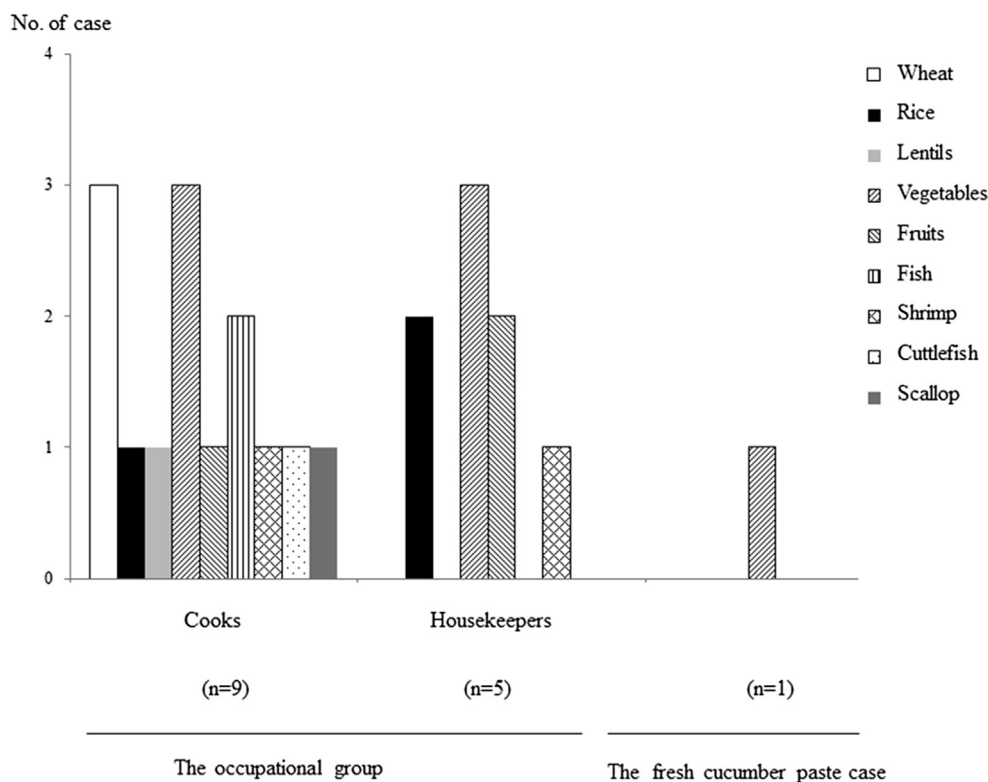


Fig. 2. The causative foods in food allergy induced by epicutaneous sensitization. In the occupational group, the foods that induced symptoms after ingestion included rice, wheat, fruits, vegetables, fish, crustaceans, and mollusk; in the fresh cucumber paste case, the cause was cucumber.

Other concomitant diseases

In terms of patients' other medical history, in the occupational group, atopic dermatitis (AD) was most frequent (9/14, 64.2%; Fig. 4). Two of 5 patients without AD suffered from hand eczema. In addition, 30% of cooks (3/9) and 66% of housekeepers (3/5) had a history of pollinosis. The patient sensitized to fresh cucumber by face pack had a history of atopic dermatitis and pollinosis to timothy-grass and ragweed.

Discussion

We elucidated several clinical features of 15 adult patients with food allergies that may have been induced by epicutaneous sensitization, including the suspected opportunity for epicutaneous sensitization, causative foods, clinical symptoms, and relevant concomitant diseases.

In this study, patients were divided into two groups based on the opportunity for preceding contact urticaria to foods: an occupational

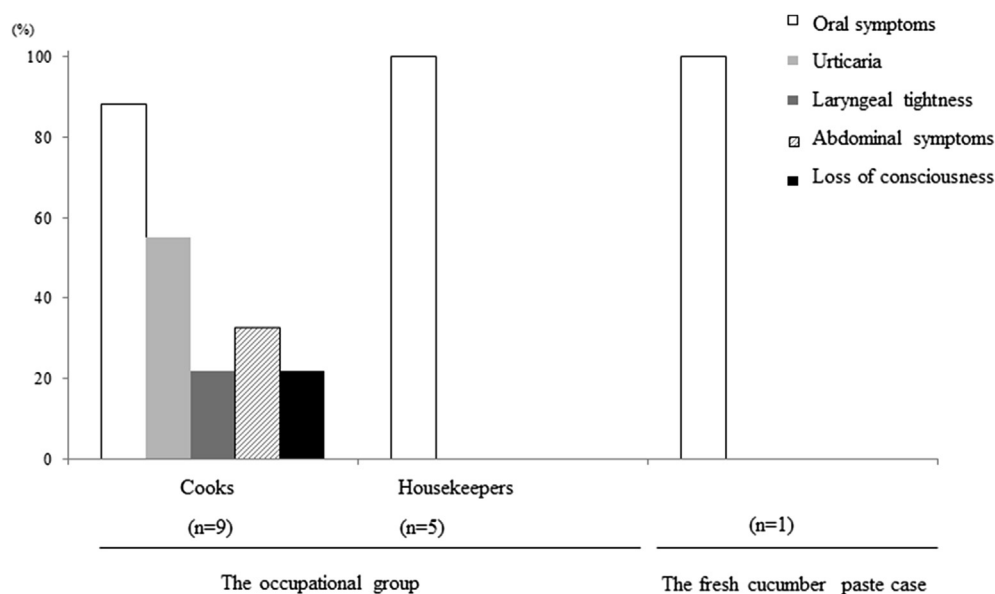


Fig. 3. Clinical symptoms after ingestion of the causative foods. The main symptoms after ingestion were oral in almost all patients (14/15, 93.3%).

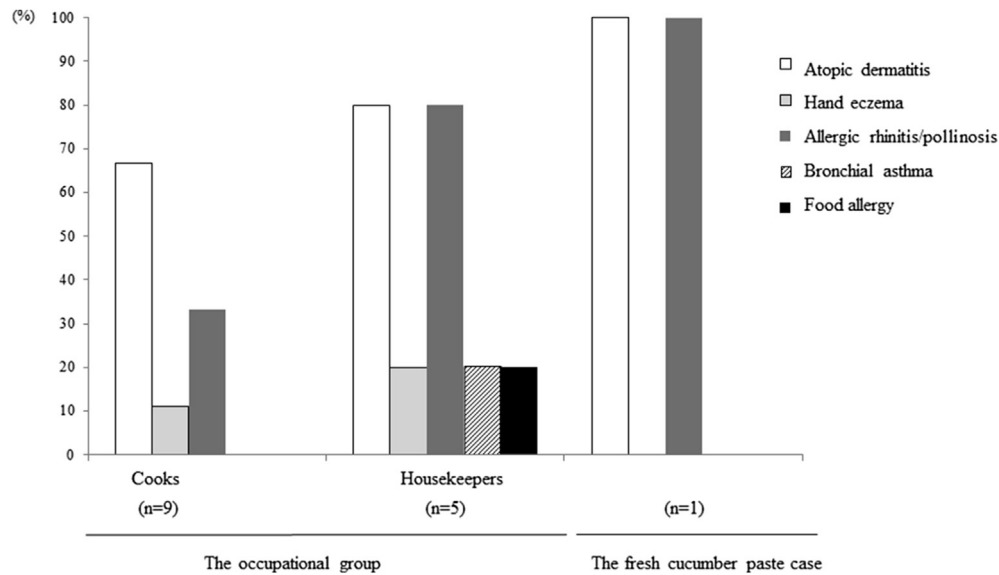


Fig. 4. Other concomitant diseases. In the 14 patients of the occupational group, 9 (64.2%), 2 (14.2%) and 6 patients (42.9%) had atopic dermatitis, hand eczema and allergic rhinitis/pollinosis, respectively. The fresh cucumber paste case had a history of atopic dermatitis and pollinosis.

group related to cooking and a fresh cucumber paste case. The situation of both groups involved daily exposure of the skin to the allergic foods or food proteins. The occupational group included sushi cooks, an Italian cook, bakers, and housekeepers. One patient was suspected to be sensitized to cucumber through face pack with fresh cucumber paste. The length of time between when subjects started jobs or using the face pack and the onset of contact urticaria was more than 1 year in all 15 patients. On the other hand, the duration between the onset of contact urticaria and the onset of food allergy was relatively short. Seven patients realized allergic symptoms after ingestion of food within a few weeks after the onset of contact urticaria. Therefore, they may have complained not only of episodes of food allergies but also of contact urticaria in interviews because of this short duration. The difference in duration in patients might have depended on the amount of allergen exposure, characteristics of allergens (e.g., protease activity), frequency of exposure, allergen forms (e.g., solution, powder, solid, etc.), or severity of the impaired skin barrier function.

The causative foods in this study covered a wide range of biological classifications, including cereals, vegetables, fruits, crustaceans, and mollusk, especially in the case of the cooks. Several previous reports have also described cases in which food allergies were preceded by contact urticaria due to the same foods. Tree nuts and garlic have been reported to be causative foods to which patients were sensitized through the epicutaneous route, resulting in the onset of a food allergy.^{11–13} In one study, allergy upon first ingestion of pine nuts was observed after onset of contact urticaria in a 28-year-old man.¹¹ In the patient, allergy to almonds was preceded by years of almond-induced contact urticaria, and the patient subsequently developed anaphylaxis due to pine nut; this was attributed to cross-reactivity between almonds and pine nuts.¹²

In this study, some patients reacted to several causative foods, whether they belonged to the same biological classification or not. Two patients (Cases 1 and 2) with allergies to fish and seafood in this study were sensitized to many kinds of fish. In Case 2, specific IgE to the purified parvalbumin of cod fish (Gad c 1), which is the major, well-known fish allergen, was detected in ELISA, suggesting that the patient could develop allergic reactions to several fish due to cross-reactivity of parvalbumin contained in fish.⁸ Three other patients (Cases 6, 7 and 11) also experienced allergic reactions after ingestion of several vegetables and fruits. Further investigation is

needed to clarify whether these symptoms were induced due to cross-reactivity between the plant-derived foods. As additional 5 patients (Cases 5, 11, 13 and 14 of the occupational group, and Case 16) had plant-derived food allergy and pollinosis, it would also be worthwhile to investigate whether food allergens might be cross-reactive to sensitized pollen allergens.

Except for fish and other seafood, it was uncooked foods that induced allergic symptoms after ingestion, whereas the foods if cooked were often tolerable in the occupational group, suggesting that the causative allergens may be not heat-stable. Such a clinical manifestation as intolerance to raw foods after ingestion has been also seen in the patients sensitized to causative foods via the inhalation route.¹⁴ Patients with baker's asthma, which is induced by the inhalation of raw wheat flour, never have problems with ingestion of cooked wheat.¹⁵ However, some of them may develop symptoms other than respiratory symptoms after ingesting meals contaminated by uncooked wheat flour. This was true of three of our patients (Cases 4, 8, and 9) in the occupational group of this study.

Oral symptoms appeared in almost all patients (13/14 patients, 92.9%) in the occupational group, making this the main symptom in this group. The fresh cucumber paste case also experienced oral symptoms after ingestion of fresh cucumber. Thus, epicutaneous sensitization to non-processed foods could induce oral symptoms after ingestion of them. However, the cook sensitized to fish (Case 2) experienced repeated allergic episodes and consequently developed anaphylactic shock after ingestion of fish. In previous reported cases of food allergies preceded by epicutaneous sensitization, symptoms induced after ingestion were also relatively severe. A 19-year-old man with a prior episode of contact and generalized urticaria after handling pine nuts developed facial angioedema, acute rhino-conjunctivitis, and asthma rapidly after the first ingestion of pasta with pesto sauce containing pine nuts.¹¹ Another patient suspected of being sensitized to almond via the skin route, developed not only angioedema on the oropharynx, face, and genitals, but also dysphagia, difficulty breathing, rash on the trunk and extremities, and dizziness.¹² Accordingly, it is possible for epicutaneous sensitization to foods to induce anaphylactic reactions after ingestion of them.

Interestingly, most patients' medical history (12/15, 80.0%) included atopic dermatitis or hand eczema. Their skin barrier, especially the epidermal barrier exposed to foods, was likely

disrupted due not only to genetic factors, but also to environmental ones, such as frequent hand washing and exposure to detergents. In the fresh cucumber paste case, the face pack was applied on the skin scrubbed. The result might be that the food proteins were able to easily pass through the impaired skin barrier and sensitize via the skin route. In 2008, Lack postulated a new “dual-allergen exposure hypothesis” that suggested ingestion of food promotes immune tolerance to food antigens, whereas exposure to food antigens through skin facilitates allergic sensitization.¹⁶ Several lines of evidence support that hypothesis, including the fact that loss-of-function variants in the filaggrin gene (*FLG*) are a significant risk factor not only for atopic dermatitis but also for peanut allergy.¹⁷ Filaggrin, an epidermal structural protein, is expressed only in the skin, not in the intestinal wall or bronchi, suggesting that impaired barrier function of the skin but not of the intestine may facilitate epicutaneous uptake of antigen and lead to allergic sensitization. In animal models, epicutaneous exposure to ovalbumin is able to induce egg allergy, and similar results have been obtained by the epicutaneous exposure to completely different food allergens, namely peanuts and cashew nuts, suggesting that the sensitization process, albeit allergen-specific, follows a common pathway irrespective of the sensitizing food.^{5,18,19} The molecular mechanism for uptake of large antigens from the outside of the skin has been previously suggested by the results of experiments in mice. To induce epicutaneous sensitization to protein antigens in mice, the stratum corneum barrier needs to be mechanically impaired by tape-stripping, acetone treatment, or patch dressing.²⁰ Tape-stripping activates Langerhans cells in ear skin of the mouse and induces penetration of the tight junction barrier by dendrites of Langerhans cells, suggesting that causing physical stress to the stratum corneum induces danger signals in the epidermis that directly or indirectly activate Langerhans cells.^{21–27} Thereafter, Langerhans cells elongate their dendrites to penetrate through tight junctions upon activation and to allow uptake of large antigens, such as ovalbumin, which has a molecular weight of 45 kDa, from the extra-tight junction environment.²¹ Thus, impairment of the stratum corneum barrier not only allows allergen penetration throughout this barrier, but also triggers the activation of Langerhans cells and facilitates subsequent uptake of antigens by Langerhans cells across the epidermal tight junction barrier. After antigen acquisition, Langerhans cells presumably migrate to draining lymph nodes and activate antigen-specific T cells, thereby facilitating epicutaneous sensitization.

The results of the present study indicated that epicutaneous sensitization of food could occur and involve food allergies under occupational cooking and skin care with foods in adults. However, we did not exclude the possibility that subjects may have already been sensitized with food protein, and simultaneously sensitized via the gastrointestinal tract. Further investigations in large-population studies will be needed to understand more precisely the manifestations of food allergies induced by epicutaneous sensitization.

Conflict of interest

The authors have no conflict of interest to declare.

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