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Two Cases of Occupational Contact Urticaria Caused by Percutaneous Sensitization to Parvalbumin

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Key Words
Contact urticaria · Occupational allergy · Percutaneous sensitization · Parvalbumin

Abstract
Background: In recent years, it has been proposed that the primary mechanism for the development of food allergies is percutaneous sensitization. Since 2010, in Japan, the number of immediate-type wheat allergy due to hydrolyzed wheat protein has dramatically increased among those who have been using soap containing hydrolyzed wheat. This incidence supports the hypothesis that food allergens arise through percutaneous sensitization. ***Clinical Summary:*** A 25-year-old man (case 1) and an 18-year-old girl (case 2) with atopic dermatitis visited our Department because of food allergy and hand eczema. After starting their work with fish, severe itchy eczema appeared on their hands. They subsequently started to experience oral allergic symptoms, intraoral itchiness and dyspnea after eating fish. Specific IgE antibodies were detected for many fishes, and skin prick tests showed positive reactions for a variety of fishes in both cases. Furthermore, the fluorescence intensities of specific IgE antibodies against parvalbumin from various types of fish in microarray immunoassay analysis showed positive reactions. We diagnosed them as contact urticaria caused by percutaneous sensitization to parvalbumin through job-related physical contact with fish. ***Conclusion:*** The patients' histories and findings indicate the possibility of percutaneous sensitization through occupational exposure to parvalbumin, leading to food allergy.

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Introduction

In recent years, it has been proposed that the primary mechanism for the development of food allergies is percutaneous sensitization [1, 2]. Since 2010, in Japan, the number of immediate-type wheat allergy due to hydrolyzed wheat protein has dramatically increased among those who have been using soap containing hydrolyzed wheat. This incidence supports the hypothesis that food allergens arise through percutaneous sensitization [3, 4].

Here, we report 2 cases of fish-induced contact urticaria that developed in patients with atopic dermatitis. Both patients gave informed consent, and this study was approved by the Ethics Committee of the authors' affiliated institution.

Case 1

A 25-year-old man with atopic dermatitis visited our Department because of food allergy and hand eczema. The patient had started working as a cook at the age of 18 years and handled various types of raw fish with his bare hands every day. After starting this work, severe itchy eczema appeared on his hands. He subsequently started to experience oral allergic symptoms, intraoral itchiness and dyspnea after eating fish. Total immunoglobulin E (IgE) antibody level was 704 IU/ml and specific IgE antibody levels (CAP fluorescent enzyme immunoassay, Phadia Inc, Tokyo, Japan) were as follows: house dust, class 2 (1.99 UA/ml); house dust mites, class 2 (1.96 UA/ml); horse mackerel, class 3 (6.10 UA/ml); flounder, class 3 (5.97 UA/ml); salmon, class 3 (5.39 UA/ml); cod, class 3 (4.23 UA/ml); sardines, class 3 (4.16 UA/ml); mackerel, class 2 (2.35 UA/ml); tuna, class 2 (1.32 UA/ml), and *Anisakis*, class 3 (14.6 UA/ml). Skin prick tests (SPT) showed positive reactions to tuna, salmon, flounder, yellowtail, and *Anisakis*, but negative reactions to squid and deep-water shrimp. The positive control (1% of histamine dihydrochloride, Wako Pure Chemical Industries, Ltd., Osaka, Japan) exhibited a reaction of 5 × 4 mm. The negative control (physiological saline) exhibited no reaction.

Sample solutions (1 μg/ml) from each type of fish were immobilized onto a microplate to perform enzyme-linked immunosorbent assay (ELISA). Positive reactions to multiple types of fish were observed in this assay (fig. 1). Furthermore, the fluorescence intensities of specific IgE antibodies against parvalbumin from various types of fish in microarray immunoassay analysis (Immuno Solid-phase Allergen Chip, ISAC®; ThermoFisher, Uppsala, Sweden) showed positive reactions (table 1) [5].

Case 2

An 18-year-old girl with a history of atopic dermatitis and pollinosis visited our department with a chief complaint of urticaria that appeared after eating fish. The patient started working at a sushi restaurant at the age of 16 years. After starting this job, she began to experience itching of her hands upon touching fish. From the age of 17 years, urticaria started to appear after eating fish. Furthermore, she experienced an episode of whole-body itching, facial edema, dyspnea, and decreased blood pressure that appeared 30 min after eating rolled sushi that contained fresh-water eel, cucumber, and lettuce. Total IgE antibody level was 474 IU/ml, and specific IgE antibody levels were as follows: horse mackerel, class 3 (10.7 UA/ml); flounder, class 3 (8.58 UA/ml); cod, class 3 (7.26 UA/ml); sardines, class 3 (7.07 UA/ml); mackerel, class 3 (6.40 UA/ml); tuna, class 3 (3.61 UA/ml), and *Anisakis*, class

0 (<0.35 UA/ml). SPT and scratch tests exhibited positive reactions for salt-water eel, salmon, sea bream, mackerel, yellowtail, and flatfish, and negative reactions for tuna, shrimp, squid, and *Anisakis*. Microarray immunoassay analyses demonstrated reactions against parvalbumin in this case as well (table 1).

Discussion

As a mechanism underlying the onset of food allergies, in 2008, Lack [1] proposed the concept that oral antigen exposure promoted more immunotolerance compared with sensitization and that percutaneous exposure affected sensitization. In an experiment on mice, a report noted that specific IgE antibodies were produced when scratched skin was exposed to peanuts [2]. Furthermore, case reports of immediate wheat allergy that had developed from percutaneous sensitization caused by hydrolyzed wheat flour in soap (Glupearl 19S) supported the idea that food allergies may be caused by percutaneous sensitization [3, 4]. This reaction was considered to occur through a multi-step mechanism: repeated face washing with this particular soap led to decreased skin barrier function, which facilitated percutaneous absorption of hydrolyzed wheat. This consequently led to sensitization.

In the present cases, both patients had atopic dermatitis in addition to jobs that entailed touching various types of fish with their bare hands that had decreased skin barrier function. It is likely that the patients' fingers were moist when handling fish, potentially creating an ideal environment for antigen proteins to be absorbed through the skin and eventually leading to percutaneous sensitization to fish. Furthermore, we postulated that oral tolerance was abrogated due to the skin being in frequent contact with the causative antigen. As a result, systemic allergy developed immediately after eating fish.

In work-related allergic reactions as seen in the present cases, avoiding exposure to allergens after onset is difficult. A career change may thus be unavoidable. Both patients in this report have discontinued work involving contact with fish and have switched to different occupations. We believe that when patients with decreased skin barrier function such as atopic dermatitis and hand eczema select an occupation that requires handling of food with bare hands, guidance must be provided on proper skincare and on protection through wearing gloves in order to prevent percutaneous sensitization to allergens.

Based on skin test and ELISA results, the present cases were diagnosed with immediate allergy via IgE antibody against multiple types of fish. Furthermore, microarray immunoassay analyses identified the antigen as parvalbumin. Parvalbumin is a heat-stable, calcium-binding protein present in the muscle of nearly all types of fish. Cross-reaction is observed among several different types of fish, so once an individual becomes sensitized to this protein, they will exhibit allergic reactions to multiple types of fish [6, 7]. Onesimo et al. [8] reported a case of contact urticaria involving specific IgE antibodies to parvalbumin. Hilger et al. [9] reported a case of near-fatal IgE-mediated anaphylactic reaction that developed within minutes of eating fried frog legs in an adult. Although they defined parvalbumin as the causative antigen, they did not mention the mechanism of pathogenesis (e.g. epicutaneous sensitization).

SPT is a useful diagnostic method for identifying immediate allergy, and crude as well as recombinant antigens have recently become commercially available. However, limitations exist to the number of test reagents. In contrast, microarray immunoassay analysis comprehensively detects specific IgEs against multiple allergens and can extensively ascertain cross-reactivity. This method proved extremely useful in determining the pathology of patients

who exhibit allergic reactions to multiple types of fish due to the presence of pan-allergen, as seen in the present 2 cases.

We have reported 2 cases of contact urticaria caused by percutaneous sensitization to parvalbumin through job-related physical contact with fish. The exact pathology of food allergy through epicutaneous sensitization remains largely unknown, and further data need to be accumulated to elucidate the underlying mechanisms.

Statement of Ethics

The patients have provided permission to publish the details of their cases, and the identity of the patients has been protected.

Disclosure Statement

The authors declare no conflicts of interest. No funding was received for this study.

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Table 1. Results from microarray immunoassay analyses

	Allergen	Protein	Case 1		Case 2	
			ISU	class	ISU	class
Carp	Cyp c 1	Parvalbumin	2.2	2	17.8	3
Cod	Gad c 1	Parvalbumin	2.3	2	7.6	2
Chicken egg	Gal d 3	Conalbumin	1.1	2	0	0
Chicken egg	Gal d 5	Serum albumin	0	0	7.6	2
Anisakis	Ani s 1	–	0	0	0	0
Anisakis	Ani s 3	Tropomyosin	0	0	0	0
Shrimp	Pen a 1	Tropomyosin	0	0	0	0
Shrimp	Pen i 1	Tropomyosin	0	0	0	0
Shrimp	Pen m 1	Tropomyosin	0	0	0	0
D. pteronyssinus (house dust mites)	Der p 10	Tropomyosin	0	0	0	0
Cockroach	Bla g 7	Tropomyosin	0	0	0	0
Timothy grass	Phl p 5	Poaceae group 5	1.6	2	0	0
Timothy grass	Phl p 7	Ca2+-binding protein	0	0	0.5	1
Cryptomeria	Cry j 1	Pectate lyase	5.3	2	56.6	3
Arizona cypress	Cup a 1	Pectate lyase	3.1	2	14.8	2
Olive	Ole e 1	Trypsin inhibitor	0	0	0.8	1
Platanus	Pla a 2	Polygalacturonase	0	0	1.2	2
Ragweed	Amb a 1	Pectate lyase	0	0	0.4	1
Mugwort	Art v 1	Defensin	0	0	5.4	2
Mugwort	Art v 3	LTP	0	0	1.4	2

Both cases 1 and 2 exhibited positive reactions to parvalbumin. The results reflect the history of pollinosis in case 2, who exhibited positive reactions to pollen antigens such as *Cryptomeria* and Arizona cypress. ISU = ISAC standardized units.

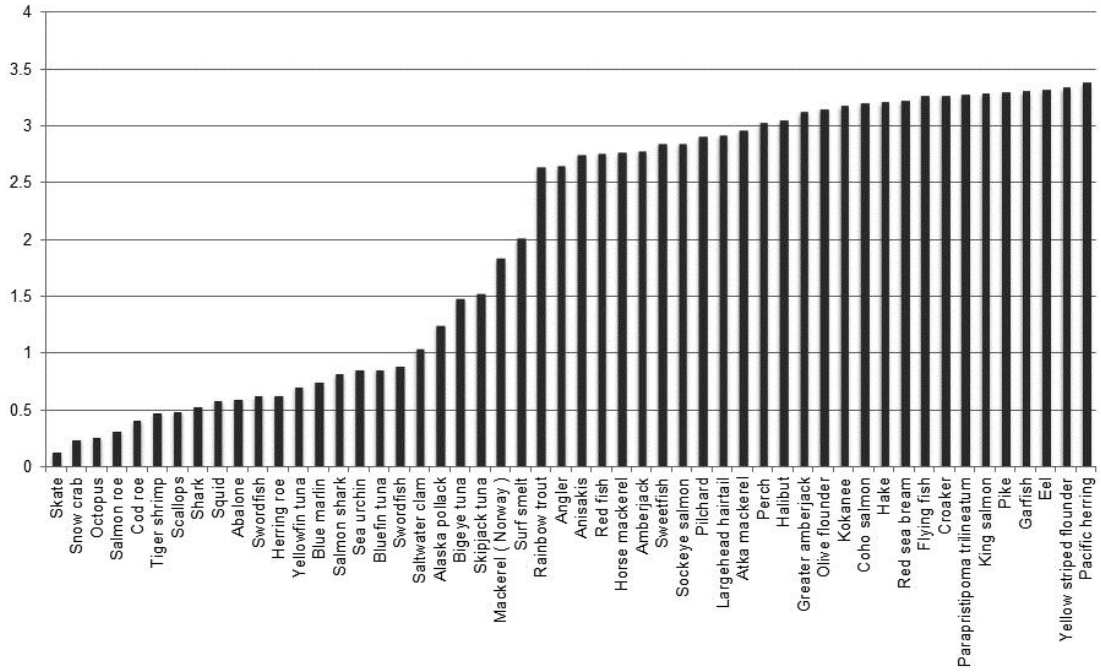

Fig. 1. ELISA results from case 1. We were using the same methods as Kondo et al. [10]. Positive reactions to various types of fish, including those that induce symptoms in the patient.