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A case of urticaria due to natto, fermented soybeans

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Dear Editor,

Natto is a traditional Japanese food of fermented soybeans, in which *Bacillus subtilis* produces natto-mucilage as metabolic product. Different from soy allergy, natto-mucilage has been reported as a cause of natto-induced late-onset anaphylaxis occurring 5-12 hours after ingestion.^{1,2}

Anaphylaxis was the primary clinical manifestation reported in natto-induced hypersensitivity.¹⁻³

Here, we report that natto can cause urticaria as a sole symptom without developing into anaphylaxis.

A 18-year-old female had suffered from chronic urticaria since childhood. She developed an anaphylaxis with decreased blood pressure, generalized urticaria, dyspnea, and palpitation 16 hours after ingesting natto at age 16. Subsequently, the urticaria became aggravated and appeared almost daily for 9 months, sometimes accompanied by mild dyspnea. Her weekly urticaria activity score (UAS7) was 28-points.⁴ She habitually consumed natto for breakfast and urticaria often occurred during daytime.

Blood tests revealed that total serum IgE was 23 IU/mL. Specific IgE antibodies against milk

were detected, but not against other tested food allergens ingested within half a day of anaphylactic episodes (Table S1). A scratch test⁴ was positive to soybeans (Torii Pharmaceutical, Tokyo, Japan), and natto-mucilage (Takanofoods, Ibaragi, Japan) was negative at 15 minutes (Figure 1). However, the reaction to only natto-mucilage became more pronounced 3 hours after the test, while only scratch marks remained at the other test sites (Figure 2). Three control patients with chronic urticaria showed no such reactions. Furthermore, basophil activation test (BAT) against natto-mucilage indicated CD203c up-regulation (48.4 %) in basophils.

Based on her eating habit and symptom seemingly-unrelated to food ingestion, we suspected that natto, not soybeans, contributed to her urticaria. Indeed, the patient experienced only slight itching but did not develop wheals after eating soybeans. Since poly γ -glutamic acid (PGA), a polymer of D- and L-glutamic acids,⁵ was reported as the main allergen of natto-mucilage¹, we instructed her to avoid natto and PGA-containing foods. This resulted in complete remission except for transient itch felt only after eating soybeans and no subsequent recurrence. Together with positive result from BAT, natto was considered as a cause of urticaria though there was a limitation of no performed oral challenge.

The skin reaction specifically observed to natto in the late phase was consistent with gradually-enhancing and long-lasting reaction after skin test previously reported in natto-induced anaphylaxis.^{1,2} Direct exposure to natto-mucilage mediated immediate basophil reactions *in vitro* but had a gradual effect in skin test *in vivo*, although both tests were supposed to assess IgE-mediated immediate reactions. The reason for this gap is currently unknown but might be associated with late-onset phenotype uniquely observed in natto-hypersensitivity. The delayed reaction in skin tests might be one of the characteristics of this allergy.

PGA sensitization may develop by stings by jellyfish nematocysts containing PGA or by oral ingestion of natto itself.^{1,3} Besides, natto consumption is increasing and PGA is widely used in various consumable products.⁵ Therefore, many people around the world are at risk of developing natto/PGA hypersensitivity. Our case suggested that clinicians should consider natto/PGA as one cause of urticaria as well as anaphylaxis.

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Figure Legends

Figure 1. Scratch test results at 15 minutes after scratching

A scratch test was performed with lancet needles and evaluated at 15 minutes. Histamine dihydrochloride (10 mg/mL) and physiological saline were used as positive and negative controls, respectively. At 15 minutes, the mean diameters of wheal and erythema for natto were 0 and 3 mm; 4.5 and 7.5 mm for soybeans, and 8 and 16 mm for histamine. Saline showed no reaction. It

was judged negative for natto-mucilage and positive for soybeans, based on the recommendations of the American Academy of Asthma, Allergy and Immunology and American College of Allergy, Asthma, and Immunology that defines a positive result as mean wheal diameters of ≥ 3 mm.⁴

Figure 2. Skin reactions of the scratch areas along time course

The scratch area of all antigens from scratch to 5 hours are shown along time course. The reaction to natto-mucilage became prominent 3 hours after scratch with wheal and erythema diameters of 5 and 18 mm, respectively. Saline had no response throughout the course.

Natto-mucilage

Soybeans

Histamine

Saline



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Figure 1

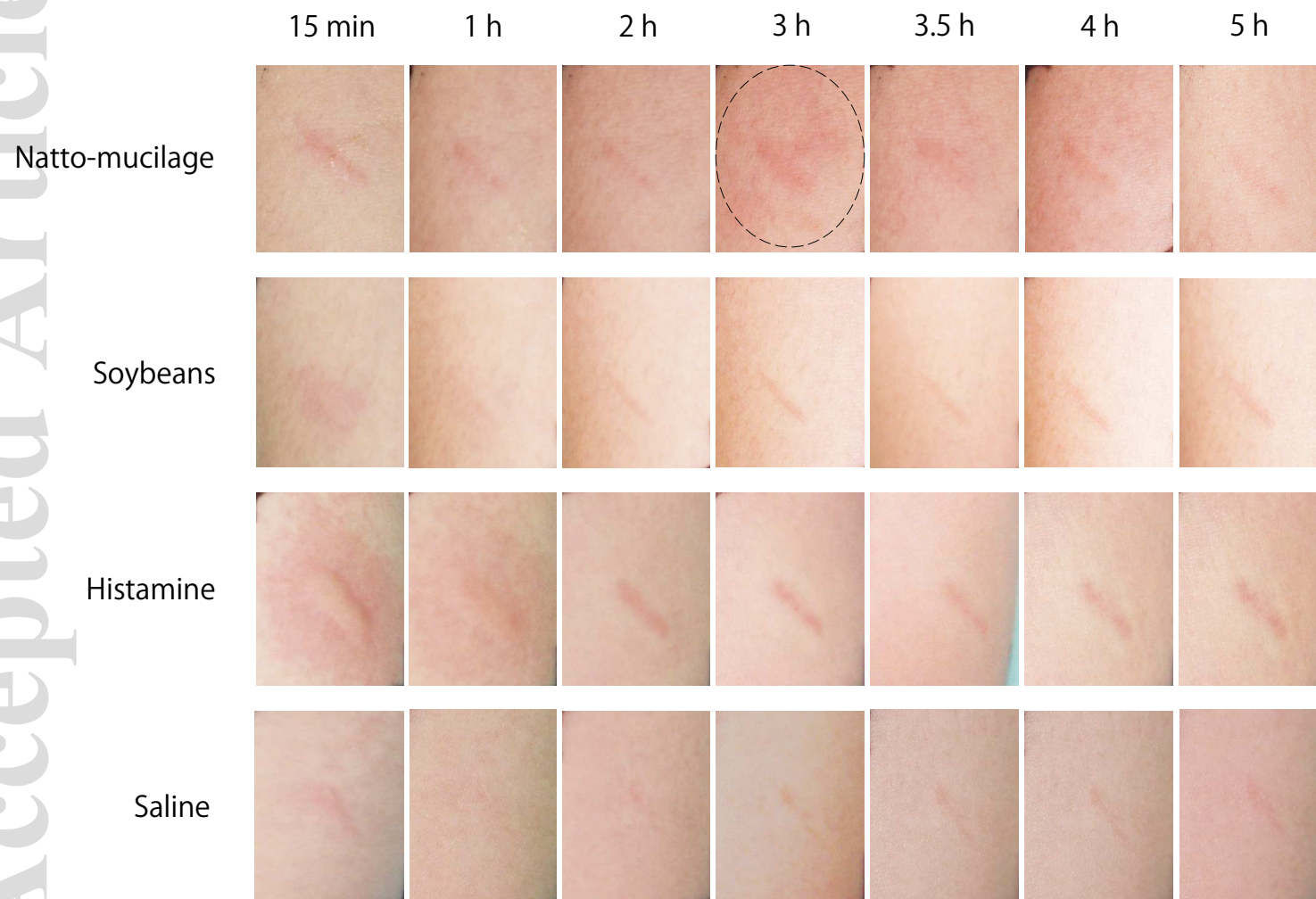


Table S1. List of antigens for specific IgE antibodies tested in this case

Dermatophagoides	Timothy	Wheat	Tuna
House dust	Ragweed	Buckwheat	Salmon
Dog	Mugwort	Rice	Mackerel
Cat	Candida	Soybean	Apple
Moth	Alternaria	Peanuts	Peach
Cockroach	Aspergillus	Shrimp	Kiwi
Birch	Malassezia	Crab	Banana
Alder	Latex	Chicken meat	Tomato
Japanese cedar	Egg white	Beef	Sesame
Cypress	Ovomucoid	Pork	Anisakis