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Letter to the Editor

Anaphylaxis from nattokinase in a patient with fermented soybean (natto) allergy

Dear Editor,

Natto, soybeans fermented by *Bacillus subtilis* var. *natto*, is a common traditional food that is widely consumed in Japan. Natto comprises two components: the soybeans themselves, and sticky mucilage that envelops the soybeans.¹ In general, patients with natto allergy show late-onset natto-induced allergic reactions/anaphylaxis.² Importantly, those patients do not show allergy to soybeans, and a major allergen is considered to be poly- γ -glutamic acid (PGA), a polypeptide contained in mucilage, but not in natto soybeans.^{3,4} Marine activities including surfing are one of the risk factors for developing natto allergy, as percutaneous injection of PGA by jellyfish stings causes systemic sensitization.^{5,6} We report herein a case of natto-induced immediate-onset anaphylaxis in a patient with no habits involving marine activities. The patient showed positive skin prick test (SPT) reactions to natto and natto mucilage, but not to PGA. Consequently, the patient was found to have been sensitized to nattokinase (NK; scientific name, subtilisin NAT), which is produced by *B. subtilis* var. *natto* and abundantly present in mucilage.⁷

A 51-year-old Japanese man was referred to our dermatology department due to several episodes of anaphylaxis over the preceding 3 months. He developed anaphylactic symptoms approximately 10 min after having natto and required emergency care. Anaphylactic symptoms included urticarial rash, hypotension, tingling of the mouth, abdominal cramps, nausea, vomiting, diarrhea, and sometimes fainting. He had never gone surfing or participated in other marine activities. He worked in the construction industry but not for detergent factories or natto factories. His medical history included mild atopic dermatitis. He also had a history of angina pectoris, for which he had started daily oral aspirin 3 months earlier. He had not experienced any anaphylactic reactions to soybeans themselves or soybean products other than natto, including soy source/miso; another soybean product fermented with *Aspergillus sojae* or *Aspergillus oryzae*, tofu (soybean curd), or soy milk. The serum total immunoglobulin (Ig)E level was 670 IU/mL (normal range, <170 IU/mL). Capsulated hydrophilic carrier polymer (CAP)-fluorescence enzyme immunoassay showed negative results for specific IgE against soybean whole allergen, Gly m 4, birch pollen extract, and alder pollen extract; the latter two are known to cause soybean-associated pollen-food allergy syndrome.⁸ SPTs were evaluated at 15 min according to the criteria of the European Academy of Allergology and Clinical Immunology⁹ and yielded positive results for whole natto (Okamenatto; Takanofoods, Ibaragi, Japan)

and natto mucilage, but negative results for soy milk and the negative saline control. To further investigate the culprit allergens in mucilage, we performed SPTs using other mucilage components: PGA (0.01%, 0.1%, and 1% in saline; Sigma–Aldrich, St. Louis, MO, USA), oligosaccharide (10% in saline; Fujifilm Wako Pure Chemical, Osaka, Japan), levan (5% in saline; Sigma–Aldrich), inulin (10% in saline; Tokyo Chemical Industry, Tokyo, Japan), and NK (0.01%, 0.1%, 1%, and 10% in saline; Fujifilm Wako Pure Chemical).¹⁰ Among these, only NK provoked a positive skin reaction in the patient (Table 1; Fig. 1), while negative reaction was noted in three patients without natto allergy. Furthermore, in basophil activation tests (BATs), NK, but not PGA, resulted in enhanced basophil CD203c expression (positive control, 19.0%; negative control, 2.9%; 10 μ g/mL NK, 20.3%; 100 μ g/mL NK, 28.0%; 1000 μ g/mL NK, 57.1%). These results indicated that the natto allergy in this patient appeared attributable to specific IgE against NK.

Patients with natto allergy often show late-onset anaphylaxis, since the major allergen in natto PGA is a water-soluble, high-molecular weight polymer (ranging from 100 kDa to more than 1000 kDa) that is slowly biodegraded in the bowels.^{1–4,10} In contrast, NK is a serine protease with a molecular weight of approximately 27.7 kDa,⁷ which is more easily absorbed in the gut than PGA.

NK is not only found in natto but also used as an ingredient in some cosmetics and dietary supplements; patients should pay

Table 1
Results of skin prick tests.

Allergen	The maximum wheal diameter (mm)
Histamine dihydrochloride (10 mg/mL)	5
Saline as the negative control	0
Fermented soybeans (natto)	4 [†]
Natto mucilage	7 [†]
Soy milk	0
PGA (1%)	0
PGA (0.1%)	0
PGA (0.01%)	0
Oligosaccharide (10%)	2
Levan (5%)	2
Inulin (5%)	2
NK (10%)	15 [†]
NK (1%)	5 [†]
NK (0.1%)	5 [†]
NK (0.01%)	4 [†]

The results of the skin prick tests were evaluated at 15 min with the criteria of the European Academy of Allergology and Clinical Immunology,⁹ a positive (†) being a wheal of 3 mm and more. PGA, poly- γ -glutamic acid. NK, nattokinase.

Peer review under responsibility of Japanese Society of Allergology.

<https://doi.org/10.1016/j.alit.2021.08.004>

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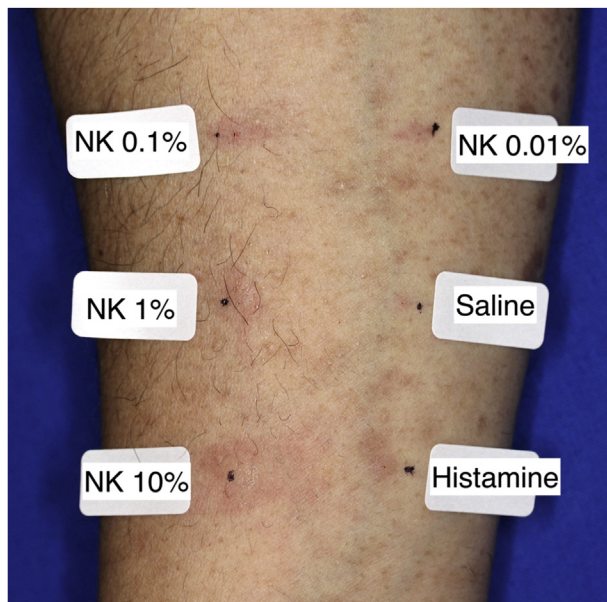


Fig. 1. Results of skin prick tests. Positive reactions are observed for nattokinase (NK).

attention to these products. The route of NK sensitization in the present case remains elusive, although he had mild atopic dermatitis, and NK sensitization is not generalizable to other cases with natto allergy. However, the possibility of NK sensitization should not be overlooked when patients show immediate-onset anaphylactic reactions against natto.

Acknowledgements

This study was partially supported by Japan Society for the Promotion of Science KAKENHI Grant-in-Aid for Scientific Research (C) (#19K08743).

Conflict of interest

The authors have no conflict of interest to declare.

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Received 20 May 2021

Received in revised form 14 July 2021

Accepted 28 July 2021

Available online xxx

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