
Adult-Onset Sheep's Milk Allergy in a Patient Without Cow's Milk Allergy

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J Investig Allergol Clin Immunol 2021; Vol. 31(3): 273-274
doi: 10.18176/jiaci.0578

Key words: Sheep's milk allergy. Percutaneous sensitization. Skin prick test. α -S2 casein. Two-dimensional electrophoresis and immunoblotting.

Palabras clave: Alergia a leche de oveja. Sensibilización percutánea. Prick test. Alfa-S2 caseína. Inmunoblotting y electroforesis bidimensional.

Most childhood-onset sheep and goat's milk allergies co-occur with cow's milk allergy because of the high sequence homology between the corresponding proteins [1]. Alvarez et al [2] reported adult-onset sheep and goat's milk allergies without cow's milk allergy. Sensitization in food allergy is traditionally considered to occur via the intestinal tract; therefore, sheep's milk allergy is mainly reported from countries with a higher consumption of goat and sheep's milk products [3]. In 2013, >2000 cases of wheat allergy in Japan were induced after sensitization by a facial soap that contained hydrolyzed wheat protein [4]. Shimojo et al [5] reported the case of a patient with fish allergy induced via percutaneous sensitization. Therefore, percutaneous sensitization is a route through which food allergies develop.

In Japan, people regularly consume cow's milk products but not sheep or goat's milk products. We report a Japanese case of adult-onset sheep's milk allergy without cow's milk allergy that was possibly induced by occupational percutaneous sensitization to sheep's milk cheese.

A 25-year-old woman with moderately severe atopic dermatitis and asthma had 3 anaphylactic episodes that were managed with injectable antihistamines and systemic corticosteroids. The patient had previously received topical corticosteroids for atopic dermatitis at a private clinic. Before the first occurrence of allergic symptoms at 21 years of age, the patient had worked regularly (6 days per week) at her part-time job for 1 year. The atopic dermatitis lesions on her hands were aggravated because she washed dishes without gloves at her workplace. Moreover, she occasionally handled pecorino cheese (made from sheep's milk) without gloves during her work. Her first anaphylactic episode occurred at 21 years of age and was associated with hand numbness, laryngeal swelling, diarrhea, and vomiting after eating pasta and bread at her workplace. At 22 years of age, the symptoms recurred after eating pasta in Italy. At age 23 years, the patient experienced sneezing, rhinorrhea,

vomiting, and facial edema after eating salad topped with grated cheese at a restaurant in Japan. She suspected her symptoms in all previous allergic episodes were due to the cheese. The patient had no allergic symptoms on consumption of cow's milk or yogurt and cheese made from cow's milk.

Her total immunoglobulin E (IgE) level was 974.0 IU/mL, and her specific IgE antibody levels (CAP-FEIA) were as follows: sheep's milk, 1.16 UA/mL; sheep's milk whey, 0.83 UA/mL; cow's milk, 0.08 UA/mL; α -lactalbumin, <0.1 UA/mL; β -lactoglobulin, <0.1 UA/mL; casein, 0.07 UA/mL; mold cheese made from cow's milk, 0.24 UA/mL; and cheese made from cow's milk, <0.1 UA/mL. We performed prick-prick tests to identify allergy-causing foods and used physiological saline and histamine dihydrochloride 10 mg/mL (Torii Pharmaceutical Co., Ltd) as negative and positive controls, respectively. We also tested commercially available pecorino cheese made from sheep's milk, sheep's milk yogurt, goat's milk, and Parmesan and Camembert cheese made from cow's milk. The patient experienced positive reactions to pecorino cheese, sheep's milk, sheep's milk yogurt, goat's milk, and histamine dihydrochloride during the prick-prick test (wheal diameter: 3.5, 5, 5.5, 3, and 6 mm, respectively), but did not react to Parmesan or Camembert cheese.

To identify causative antigens, we performed 2-dimensional electrophoresis and immunoblotting using previously reported methods with slight modifications, followed by mass spectrometry [4]. The study design for 2-dimensional electrophoresis and immunoblotting was approved by Fujita Health University (approval no. HM16-371). The IgE antibody reacted specifically with the α -S2 casein in sheep's milk in this case, compared with those in the adult negative control sample from an individual without allergy to sheep's milk or cow's milk, atopic dermatitis, or asthma. The causative protein for the patient's anaphylaxis was the α -S2 casein in sheep's milk (accession no. P04654), despite no observable IgE binding to the α -S2 casein in cow's milk (accession no. P02663) (online supplementary Figure 1).

Consistent with the clinical symptoms, antigen analysis revealed that the patient's specific IgE antibody bound to the α -S2 casein in sheep's milk but not to that in cow's milk. Different portions of the amino acid sequences of these 2 proteins were considered antigenic in this case. A comparison of the amino acid sequences of α -S2 casein from sheep's milk (accession no. P04654), cow's milk (accession no. P02663), and goat's milk (accession no. P33049) showed 89% homology for sheep's and cow's milk protein, but 98% homology for sheep's and goat's milk protein on BLAST (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>). The antigenic epitope is thought to be present in the sheep's and goat's milk only portion of the sequence. Ah-Leung et al [6] studied 28 patients with goat and sheep's milk allergies and found that 26 did not have cow's milk allergy, similar to the result in the present case. Enzyme allergosorbent tests showed that goat's or sheep's milk allergy involved the casein fraction but not whey proteins. Goat's or sheep's milk allergy occurs at older ages than cow's milk allergy, and the former is associated with more severe symptoms on ingestion of minor quantities. The patient in the present case developed anaphylactic symptoms on consuming cheese sprinkles on salad, despite daily consumption of cow's milk with no symptoms. We

considered that the patient may have been percutaneously sensitized to sheep's milk at work and that this eventually resulted in anaphylaxis. The patient had no history of ingestion of or contact with goat's milk products; therefore, the positive response to the prick-prick test with goat's milk was attributed to a cross-reaction with the α -S2 casein in sheep's milk. We recommended the patient to avoid both goat's milk and sheep's milk and products derived from these. The patient has not experienced any immediate allergic reactions to date.

The 2 mechanisms considered causes of allergy to goat's and sheep's milk are cross-reactivity to cow's milk and percutaneous sensitization to α -S2 casein in goat's or sheep's milk. As seen in this case, a patient not allergic to cow's milk and sensitized to α -S2 casein may experience severe allergic symptoms after ingesting even small quantities of goat's or sheep's milk products. Thus, even a small amount of cheese sprinkled on a salad should be considered a possible cause of anaphylaxis.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

KM is employed in an endowed department that is sponsored by Hoya Co., Ltd. The remaining authors declare that they have no conflicts of interest.

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■ Manuscript received April 30, 2020; accepted for publication August 19, 2020.

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