Anaphylaxis to Goat's and Sheep's Milk in an Adult Who Tolerated Cow's Milk: A Sensitization Profile Study

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Allergy to cow's milk (CM) is a common food allergy in children and can present with the full spectrum of IgE-mediated allergic reactions, including anaphylaxis [1]. Almost all affected individuals become tolerant by their late teenage years [2]. Most CM-allergic individuals are sensitized to casein, the main protein fraction of milk. CM proteins typically share >85% sequence homology with goat's and sheep's milk (GSM) proteins, resulting in a high degree of cross-reactivity in CM-allergic persons. Indeed, goat's milk (GM)–induced allergic reactions occur in more than 90% of CM-allergic individuals [3]. However, rare cases with specific allergy to GSM in CM-tolerant individuals have been reported [4,5]. We report the case of an adult in whom evaluation for sensitization to milk proteins revealed a very uncommon GSM-specific allergy.

A 39-year-old man presented with recurrent episodes of anaphylaxis over 20 years, with 1 episode per year on average. Reactions typically developed within minutes after eating. The episodes were of variable severity and involved severe stomach pain, urticaria, facial angioedema, and—on several occasions—anaphylactic shock. Symptoms resolved in all episodes after treatment with an epinephrine autoinjector, whereas antihistamines alone were insufficient. The patient reported that the episodes occurred after eating feta cheese, traces of GM cheese, or other GSM cheese–containing foods, although he tolerated CM cheese and large quantities of pasteurized CM without symptoms. Notwithstanding this tolerance, the patient recalled reactions after ingestion of concentrated CM-derived whey protein nutritional supplements. He has minor pollen–associated food allergy. Skin prick tests showed sensitization to GSM and GSM cheese, but not to CM or CM cheese (Fig. S1A). Total IgE was 100 IU/mL (<100) and baseline tryptase 2.2 ng/mL (<11.4). Specific IgE testing (ImmunoCAP, Thermo Fisher) revealed sIgE against whole GM (0.53 kU_A/L) and sheep's milk (SM) (0.76 kU_A/L) and against SM whey proteins (0.74 kU_A/L) (Table S1).

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Commercial sIgE tests against GM whey proteins and GM and SM caseins were not available. Levels of sIgE against whole CM (0.19 kU_A/L) and CM whey proteins (α-lactalbumin, 0.16 kU_A/L; β-lactoglobulin, 0.11 kU_A/L) were slightly above the limit of detection, while sIgE to CM caseins could not be detected (Table S1). We excluded sIgE-mediated sensitization to LTP, ω-5-gliadin, and galactose-α-1,3-galactose.

We diagnosed recurrent anaphylactic reactions to GSM products associated with tolerance to CM. To further elaborate on the target allergen and cross-reactivity profiles, we performed IgE-Western blot analyses with CM, GM, and SM. We included control sera from patients with distinct molecular sensitization profiles to milk, as follows: isolated sensitization to casein with anaphylaxis to milk from all 3 species (patient #2); sensitization to CM casein, α-lactalbumin, and β-lactoglobulin with mild CM allergy (patient #3); and isolated sensitization to bovine serum albumin with tolerance to milk (patient #4) (Table S1). The serum of patient #1 showed IgE binding to a band at 19 kDa both in GM and SM (Figure, A). This band was at the same molecular weight as the lowest band in patient #2. The known sIgE sensitization profile in patient #2 (isolated sensitization to caseins) suggests that the lowest band represents κ-casein and the remaining bands α- and β-casein. Therefore, we concluded that the band in the case we report was compatible with κ-casein. Specific binding of IgE was not inhibited following serum pre-adsorption with cow casein–loaded beads (maximal signal suppression, 21%) (Figure, B). In contrast, 80% inhibition was observed in patient #2, thus indicating cross-reactivity of IgE to CM and GSM caseins in this case.

Notably, sIgE to whey proteins in patient #1 were only detected using Western blot at high protein concentrations when using pasteurized GSM (data not shown). In contrast, Western blot analyses using fresh unpasteurized SM and separated casein and whey fractions of SM confirmed sensitization to SM whey proteins, with bands at around 15 kDa and 12 kDa, comparable to those detected in patient #3 with CM allergy and sIgE against CM α-lactalbumin and β-lactoglobulin (Figure, C). We confirmed that the milk processing temperature affects detection of IgE in Western blot also for CM, thus underpinning the relevance of the milk treatment temperatures applied in milk-specific IgE sensitization profile studies (Fig. S2). Combined, our data reveal sIgE in our patient-targeted whey proteins and κ-casein in GSM, with no detectable cross-reactivity to CM casein. The traces of sIgE against CM whey proteins detected by ImmunoCAP may explain the patient's clinical reactions to highly concentrated CM whey protein supplements and indicate dose-dependent in vivo cross-reactivity between CM and GSM whey proteins. We performed an in silico structural comparison of κ-casein, α-lactalbumins, and β-lactoglobulins from CM, SM, and GM (Supplementary data). We identified several surface-exposed amino acids unique to GSM κ-casein, which could well serve as GSM-specific epitopes (Figure, D).

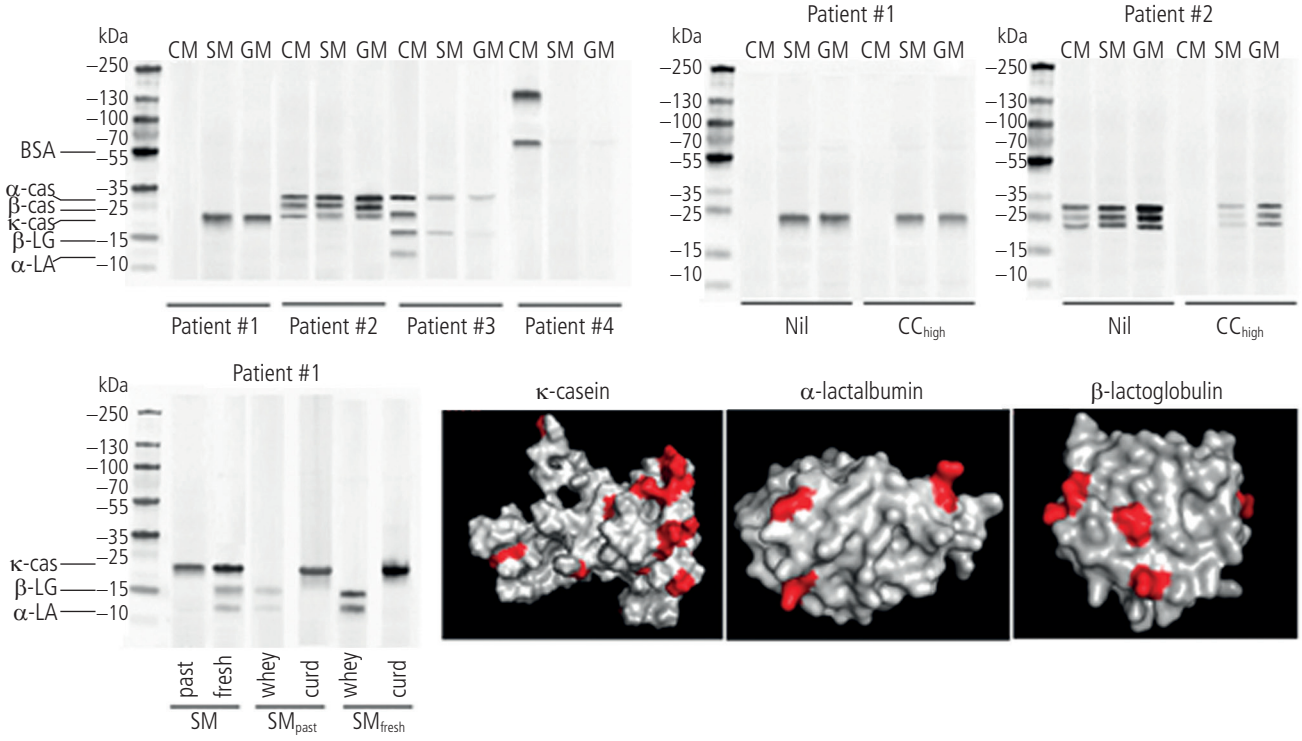

Figure. Milk sensitization profile. A, Western blot of pasteurized CM, SM, and GM using patient sera. The main milk proteins are shown on the vertical axis. B, CM pre-adsorption experiments with CM casein (CC). C, Western blot with pasteurized and unpasteurized SM and whey vs casein-containing curd fraction. D, Visualization of amino acids unique to the GSM proteins (red) as potential non-CM–cross-reactive epitopes. CM indicates cow's milk; SM, sheep's milk; GM, goat's milk.

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The whey proteins showed a higher degree of interspecies structural similarity.

To date, only a few cases of adults with GSM allergy who tolerated CM have been reported (Table S2). Molecular investigations identified sIgE against whey proteins and caseins [4,6]. GSM κ-casein was likely the main allergen in the case we report, since the patient had clinical, skin-prick-test, and IgE reactions to GSM cheese, which mainly contains caseins. The lower interspecies cross-reactivity for κ-casein than for other casein proteins [7] may explain the tolerance to CM in the case we report.

Knowledge of isolated GSM allergy is clinically relevant. GSM dairy products are important components of the human diet [8]. In high-income countries, GSM products are becoming popular foods. Moreover, casein-containing GM or SM powders are being used as nutritional supplements. In the present case, severe allergic reactions occurred with traces of GSM products, while CM was tolerated at high doses. Larger cohorts are needed to assess whether sensitization to GSM-specific κ-casein and whey protein is associated with severe anaphylaxis to GSM in general.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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