Millet: A "Gluten-free" and "Healthy" Cereal With the Potential to Induce Anaphylaxis

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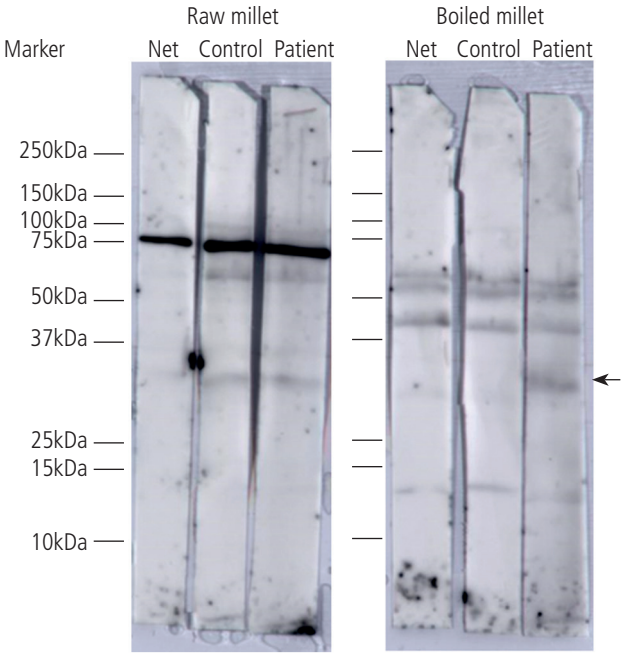

Figure. IgE immunoblot with raw and boiled millet seed extract in a 43-year-old woman.

Millet is a small, rounded cereal from the Poaceae family. It has been consumed since 2700 BC in China [1] and is currently cultivated in India, Africa, and China. Its consumption has increased in recent years owing to the popularity of "gluten-free" and "healthy" diets. It has high protein and fiber content and is used as bird food in developed countries, as well as in biscuits, drinks, weaning foods, and beer [2]. Since 1981, when Parker et al [3] reported the first case of anaphylaxis due to millet consumption, various cases have been reported. A few allergens have been identified to date, and cross-reactivity between millet and other cereals is not uncommon [1,4-10].

We present the case of a 43-year-old woman who developed globus sensation, ocular itching, tearing, eyelid and pinna edema, nasal bleeding, flushing, and palmoplantar itching that gradually became generalized after eating boiled millet seeds. She was admitted to the emergency room, where no objective change in vital signs was observed, and intravenous methylprednisolone and dexchlorpheniramine were administered, although intramuscular adrenaline would also have been a valid option for the anaphylaxis symptoms. The symptoms subsided after a few hours.

The patient was referred to our Allergology Outpatient Clinic, where she also reported having experienced constant, predominantly nocturnal cough for several months. She mentioned having 2 seed-eating budgerigars that flew freely around the house. They were fed bird food that contained millet and other seeds.

A prick-to-prick test was performed with bird food provided by the patient, budgerigar feathers, and raw and boiled millet, all of which yielded positive results. In addition, intense positive reactions were observed in the skin prick test (SPT) with grass pollen, rice, and corn, and ImmunoCAP revealed immunoglobulin E (IgE) antibodies against grass rye, barley, rice, corn, hazelnut, and budgerigar feathers (See online repository).

Based on the positive prick-to-prick test result with millet seeds, we analyzed raw and boiled millet seed extract. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) with raw and boiled millet seed extracts was performed to determine the protein bands. SDS-PAGE was followed by immunoblotting with the patient's serum and both raw and boiled millet seeds extracts, which yielded a single binding band of approximately 36 kDa in the boiled millet seed extract (Figure). The heating process may have helped express epitopes that would not have been present otherwise. The 36-kDa band was excised from the gel of SDS-PAGE with the boiled millet seed extract before being digested and analyzed using matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry at the Proteomics Department of Complutense University of Madrid. Proteins were identified by peptide mass fingerprinting using a Uniprot DB (www.uniprot.org), with taxonomy restricted to Viridiplantae. This revealed 55% homology with a globulin 1S protein, corresponding to a cupin. In order to test possible cross-reactivity between millet and grass pollen proteins, 5 individuals with typical grass (Gramineae) pollen allergy were investigated for IgE positivity against millet by performing immunoblotting with boiled millet extract. Two of the individuals recognized several bands. We cannot be sure that the bands recognized are not the same as those observed in the case we report, since the patient's serum was not included in this blotting test. One of the patients had been a bird keeper in the past, (Lane 3, Online Repository Figure 1A). In accordance with the findings of Bohle et al [1], the remainder did not recognize any millet proteins (Online Repository Figure 1A). We also performed immunoblotting in order to test IgE reactivity to grass pollen in the patient and the other 5 grass pollen–allergic individuals (Online Repository

Figure 1B). The only patterns recognized were those observed in the grass-allergic patient's serum.

We carried out basal spirometry and bronchodilatation and measured fractional exhaled nitric oxide to explore the origin of the cough. The results were normal. Nonspecific bronchial hyperresponsiveness was assessed using the methacholine challenge test, which also yielded normal results (the patient had not been exposed to the birds or the bird food in the 3 months before testing). This was followed by a specific inhalation challenge test with raw millet, which induced an allergic reaction (See online Repository).

Ours is the first report of a 36-kDa IgE-binding band identified as a globulin 1S protein in millet seeds. According to the available literature, this globulin 1S protein could be the culprit allergen [1,5,8]. In a recent publication by Bravo et al [10], 2 bands of 12 and 36 kDa were recognized by a patient with asthma and rhinitis due to millet seeds [10] (See online Repository).

Inhalation is currently thought to be a sensitization pathway, based on the observation that most published cases involve bird keepers with anaphylaxis the first time they consume millet [1,4-7]. Moreover, sensitization to millet is long-lasting despite the individual not being exposed to birds for years. Hemmer et al [6] described 9 patients with allergy to millet after consumption, 8 of whom were current or former bird keepers [6]. Cross-reactivity with other cereals has been described, although its clinical relevance is controversial [1,4-9]. In the case we report, the patient tolerated corn, rice, wheat, rye, and barley after anaphylaxis due to millet ingestion. Cross-reactivity with grass pollen has been ruled out in previous articles, a finding we supported using the boiled millet extract (Online repository Figure 1A).

Cupins are storage proteins that have been identified not only in millet, but also in corn, different species of wheat, fruits (eg, pineapple), and flowers (eg, orchids).

In conclusion, to our knowledge, this is the first case in which a globulin 1S protein has been identified as a possible millet allergen. We observed other bands that could be the same as those reported elsewhere [10]. We believe that an increase in the popularity of "healthy" and "gluten-free" diets could be accompanied by an increase the incidence of millet sensitization. Ours is the second reported case of symptoms after millet inhalation and ingestion [4], showing millet to be a potentially dangerous food in terms of allergic reactions. Therefore, we encourage screening for sensitization in atopic bird keepers.

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Conflicts of Interest

J.S. reports having served as a consultant to Thermo Fisher, MEDA, Novartis, Sanofi, Leti, Faes Farma, Mundipharma, and GSK. J.S. has also been paid lecture fees by Novartis, GSK, Stallergenes, LETI, and Faes Pharma and has received grant support for research from Thermo Fisher, Sanofi, and ALK. V.d.P. reports having served as a consultant to AstraZeneca and GSK and having been paid lecture fees by both. B.S. declares having received a grant or contract from CIBER (Respiratory Disease). M.V. declares having been paid lecture fees by GSK. The remaining authors declare that they have no conflicts of interest.

References

1. Bohle B, Hirt W, Nachbargauer P, Ebner H, Ebner C. Allergy to millet: another risk for atopic bird keepers. Allergy. 2003;58(4):325-8.
2. Woomer JS, Adedeji AA. Current applications of gluten-free grains - a review. Crit Rev Food Sci Nutr. 2021;61(1):14-24.
3. Parker JL, Yunginger JW, Swedlund HA. Anaphylaxis after ingestion of millet seeds. J Allergy Clin Immunol. 1981;67(1):78-80.
4. Stuck BA, Blum A, Klimek L, Hörmann K. Millet, a potentially life-threatening allergen. Allergy. 2001;56(4):350.
5. Kotachi M, Takahagi S, Ishii K, Hanaoka K, Tanaka A, Hide M. A case of millet allergy that developed into wheat-induced anaphylaxis by cross-reaction between millet and wheat antigens. Allergol Int. 2020;69(3):471-3.
6. Hemmer W, Sesztak-Greinecker G, Wöhrl S, Wantke F. Food allergy to millet and cross-reactivity with rice, corn and other cereals. Allergol Int. 2017;66(3):490-2.
7. Takahama H, Shimazu T. Common millet anaphylaxis: a case of a bird-keeper sensitized to millet via inhalation, who developed anaphylaxis after oral ingestion. Clin Exp Dermatol. 2008;33(3):341-2.
8. Rombold S, Ollert M, Sbornik M, Rakoski J, Darsow U, Ring J. Immediate-type respiratory allergy to millet-containing seed mixture of bird food. World Allergy Organ J. 2008;1(8):135-7.
9. Urisu A, Yamada K, Masuda S, Komada H, Wada E, Kondo Y, et al. 16-kilodalton rice protein is one of the major allergens in rice grain extract and responsible for cross-allergenicity between cereal grains in the Poaceae family. Int Arch Allergy Appl Immunol. 1991;96(3):244-52.
10. Bravo E, González Mahave I, Sola JP, Vidal Oribe I, Hernández Alfonso P, Peñalver-Mellado M. Millet Seed sensitization in a lovebird keeper. A case report. J Investig Allergol Clin Immunol. 2021;15:0.

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