

Anaphylaxis after mango fruit intake. Identification of new allergens

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Mango fruit allergy is a rare entity. *Mangifera indica* belongs to the *Anacardiaceae* family, along with pistachio and cashew [1]. Spain is the leading producer of mango in the European Union and its consumption in our country, according to data from the Tax Agency, has almost tripled in the last 5 years [2]. This data suggests that, in the coming years, we probably will see an increase in cases of mango allergy in line with the increase in its consumption.

We report a case of anaphylaxis after mango fruit intake in which thioredoxin-dependent peroxiredoxin, inositol-3-phosphate synthase, Man i 1, Man i 2, and proteins with molecular weight of 50, and 75 kDa were identified as the sensitizing allergens.

A 29-year-old male patient with no personal or family history of atopy was referred to the Allergy Department to study four episodes of symptoms suggestive of allergy after eating mango fruit. In these episodes, he developed lingual, uvula, eyelid, facial and genital angioedema as well as a generalized itchy, and erythematous rash minutes after eating mango fruit. In the last episode, he was admitted to the emergency department and received parenteral antihistamine and corticosteroid with improvement of symptoms. Therefore, the patient fulfilled the diagnosis criteria for anaphylaxis and was sent to the Allergy Department for evaluation. Written consent for publication was obtained from the patient.

After a detailed anamnesis, we concluded that the four episodes occurred minutes after the intake of mango fruit in different presentations (raw fruit, sushi containing mango, and a mango-flavoured yogurt without portions of fruit). He has tolerated all other fruits and nuts, including cashew and pistachio. In the test that we requested, the hemogram showed no alterations, measurement of IgE antibodies to mango fruit (0.01 kU/l), pistachio (0.02 kU/l), cashew (0.00 kU/l), latex (0.01 kU/l), and several recombinant allergens by ImmunoCAP

(Thermo Fisher Scientific, Uppsala, Sweden) were all negative (<0.35 kU / l) although skin prick test (prick by prick) with mango pulp was positive (4mm). Therefore, sensitization to mango pulp was confirmed by the prick test.

The patient received the indication to avoid mango fruit intake. Antihistamines, steroids, and autoinjector of adrenaline were prescribed in case of a reaction. A challenge with mango was not performed owing to the severity of the reaction and sensitization to that fruit.

In vitro experiment was performed with complete mango extract manufactured by us from the fruit of the variety “TOMMY ATKINS” defatted with ether. Then, a SDS-PAGE and an immunoblotting assay were performed. As a result, several bands were recognized by IgE from patient with the following molecular weights: 75 kDa, 60 kDa, 50 kDa, 40 kDa, 30 kDa, 23 kDa (Figure 1).

According to published data, four allergens have been described in mango pulp: Man i 1 (Glyceraldehyde 3-phosphate dehydrogenase; 40 kDa), Man i 2 (30 kDa), Man i 3 (Profilin; 14 kDa), and Man i Chitinase (46 kDa); being considered major allergens Man i 1 and Man i 2 [3]. Furthermore, in a study performed in 2010 by Paschke et al., immunoblotting was performed with the sera of 52 patients sensitized to mango and IgE binding was identified in the different sera with the following protein bands: 40 kDa, 30 kDa, 67 kDa, 43 kDa, 50 kDa, 14 kDa, 25 kDa, and 16 kDa [4].

We observed, as a previously undescribed novelty, the sensitization to mango pulp proteins of approximately 75 kDa, 60 kDa, and 23 kDa, although later could be the same described by Paschke of 25kDa [4]; in addition to sensitization to the 50 kDa protein and the Man i 1 and Man i 2 allergens. So, the bands of 23 kDa, a 60 kDa, and a 75 kDa from the mango extract were analysed by mass spectrometry using Matrix-Assisted Laser Desorption/Ionization-Time-Of-Flight (MALDI-TOF) mass spectrometry (MALDI TOF MS). Research conducted by searching a non-redundant protein sequence database (NCBI) was performed using the Mascot program (<http://www.matrixscience.com>), identified the 23-kDa protein as a thioredoxin-dependent peroxiredoxin (with a score of 161 and a protein sequence coverage of 51%), the 60 kDa band as an inositol-3-phosphate synthase (score: 312, protein sequence coverage 26%), and the 75-kDa protein as an uncharacterized protein (score: 255, protein sequence coverage: 31%). The 50 kDa, 40 kDa, and 30 kDa were not analysed because they had been described in the

previous literature [3, 4]. Peroxiredoxins and inositol phosphate synthase have multiple functions in the antioxidant defence signalling pathway of the cell [5, 6].

Based on these results, the diagnosis of allergy to mango fruit due to sensitization to Man i 1, Man i 2, thioredoxin-dependent peroxiredoxin, inositol-3-phosphate synthase, and proteins with molecular weights of 50 and 75 KDa was reached.

Although there are no specific epidemiology data on mango allergy, it is a rare but probably growing entity [7,8]. Until the present study, few mango allergens have been identified, none of them are available in the most extended diagnostic platforms in clinical practice such as ImmunoCAP™ Specific IgE and ImmunoCAP ISAC®[9].

When we attend a patient with a systemic reaction and sensitized to mango fruit, it would be interesting to consider that other proteins might be involved in the clinical case. For this reason, sometimes the study of food allergy by skin tests and the detection of specific IgE may be insufficient and is required an *in vitro* study by Immunoblotting to identify the specific proteins that cause the reaction. With the description of new allergens of mango fruit, we would like to open the field of the proteins used for the skin tests diagnosis, while also suggesting the increase in use and application of laboratory *in vitro* tests as western blot in the diagnosis of allergies. As a limitation of our study, nonetheless, we have to point that a study with more cases on this allergy can be very helpful to determine the possible use of other techniques as basotest, that could be tested for mango fruit diagnosis in a greater population. It allows us to indicate the most appropriate treatment, evaluate the cross-reactivity with other foods, and foresee the type or severity of future events.

This clinical case presents a significant contribution because it is the first time that thioredoxin-dependent peroxiredoxin, inositol-3-phosphate synthase, and an unknown 75 kDa protein have been described as mango fruit allergens.

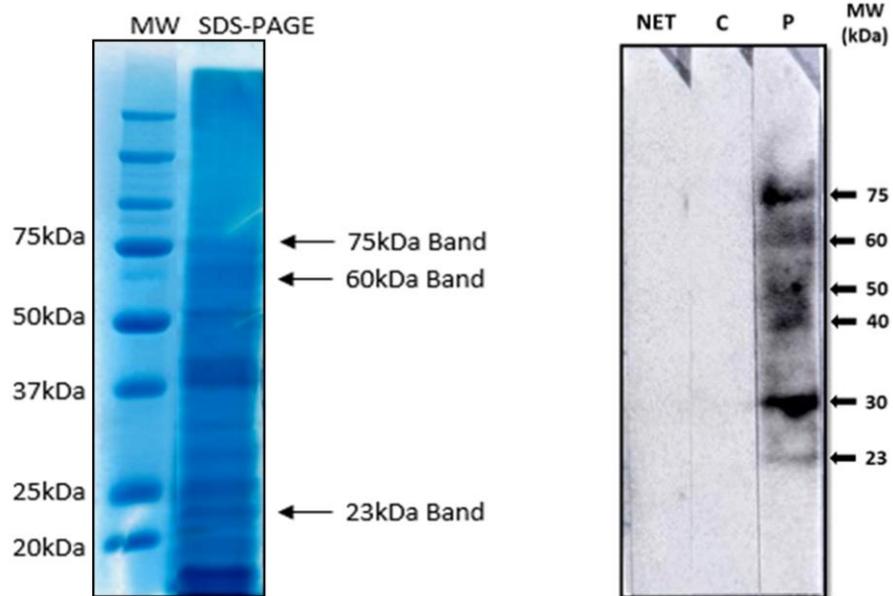
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References

1. Ukleja-Sokołowska N, Gawrońska-Ukleja E, Lis K, Żbikowska-Gotz M, Sokołowski Ł, Bartuzi Z. Anaphylactic reaction in patient allergic to mango. *Allergy Asthma Clin Immunol*. 2018;14:78.
2. Explotaciones agrícolas - Agencia Tributaria [Internet]. [cited 2021 Jul 8]. Available from: https://www.agenciatributaria.es/AEAT.internet/en_gb/Inicio/Ayuda/Manuales_Folleto_y_Videos/Manuales_practicos/IRPF/ Ayuda IRPF 2019/Capitulo 9 Rendimientos de actividades economicas estimacion objetiva II/Apendice/Explotaciones agricolas/Explotaciones agricolas.html
3. Cardona EEG, Heathcote K, Teran LM, Righetti PG, Boschetti E, D'Amato A. Novel low-abundance allergens from mango via combinatorial peptide libraries treatment: A proteomics study. *Food Chem*. 2018;269:652–60.
4. Paschke A, Kinder H, Zunker K, Wigotzki M, Weißbecher R, Vieluf D, et al. Characterization of Allergens in Mango Fruit and Ripening Dependence of the Allergenic Potency. *Food and Agricultural Immunology*. 2001;13(1):51–61.
5. Liebthal M, Maynard D, Dietz K-J. Peroxiredoxins and Redox Signaling in Plants. *Antioxid Redox Signal*. 2018;28(7):609–24.
6. Ni Y, Li G, Ji X, Yang Y, Guo X, Sun Q. Identification of an inositol-3-phosphate synthase 1-B gene (AccIPS1-B) from *Apis cerana cerana* and its role in abiotic stress. *Cell Stress Chaperones*. 2019;24(6):1101–13.
7. Clinical cross-reactivity among mango, pistachio nut, and cashew nut in allergic children - ScienceDirect [Internet]. [cited 2021 Oct 30]. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S2213219820305882?via%3Dihub>
8. Hegde V, Venkatesh Y. Anaphylaxis Following Ingestion of Mango Fruit. *J Investig Allergol Clin Immunol*. 2007;17:4.
9. Catálogo de productos para el diagnóstico de enfermedades alérgicas y autoinmunes [Internet]. Thermo Fisher Scientific. [cited 2021 Jul 8]. Available from: <https://www.thermofisher.com/phadia/es/es/product-catalog.html?solution=ImmunoCAP®ion=ES>

Figure 1. SDS-PAGE of the mango fruit extract (Left) and IgE-immunoblotting of mango fruit with patient' serum (Righ). MW, indicates molecular weight; SDS-PAGE indicates mango fruit extract; NET indicates negative control; C, nonatopic individual serum; P, patient serum.



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