Cross-reactivity in the Anacardiaceae Family: Pink Peppercorn Tolerance in a Pistachio-allergic Patient

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Tree nut allergy is one of the most common IgE-mediated food allergies, with prevalence rates varying widely from 0.05% to 4.9%. Allergy to other foods, such as egg, milk, wheat, and soy, are often resolved. However, allergy to fish, tree nut, and peanut can lead to more severe and fatal reactions [1]. The tree nut pistachio (*Pistacia vera*), with its 5 allergenic components (Pis v 1 to 5), belongs to the Anacardiaceae family, which also includes cashew, mango, and pink peppercorn (PP) [2]. Given the close phylogenetic relationship between them, cashew, mango, and pistachio exhibit different cross-reactivity rates, while PP necessitates further investigation to determine its true allergenic potential [3], owing to its emerging use in some foods, such as pepper mill mixes. Here, we report the clinical and allergological work-up for PP in a patient with pistachio allergy and Ring and Messmer grade III anaphylaxis. The patient gave his written informed consent for this case report to be published.

A 38-year-old man with comorbidities of atopic dermatitis, obesity, and coronary heart disease presented to our allergy outpatient clinic after experiencing an anaphylaxis episode. He developed nausea/emesis, urticaria, dyspnea (SpO_2 89%), hypotension (70/40 mmHg), and syncope after consuming pistachios. An emergency ambulance administered intravenous fluids (1000 mL), intravenous diphenhydramine (60 mg), intravenous prednisolone (250 mg), and oxygen (6 L/min). The patient was hospitalized for overnight observation and discharged the following morning after a visit to our allergy outpatient clinic. An allergological work-up was scheduled for 3 months later and was to include prick-to-prick testing (PTPT) with representatives of the Anacardiaceae family and other cross-reactive allergens reported in the literature but not recently consumed by the patient. PTPT revealed a positive reaction for pistachio, cashew, and PP, with wheal sizes of 7.6, 6.0, and 4.5 mm, respectively (Figure). No positive skin reaction was recorded for mango, consistent with the patient's reported history of tolerance in the meantime.

The results of the laboratory tests are shown in Supplementary Table 1. The patient had highly increased specific IgE (ImmunoCAP™, Thermo Fisher Scientific/Phadia) against pistachio and cashew, including Ana o 3. Based on the highly elevated serum tryptase level (76.8 µg/L) and a REMA score of 7 (male +1, syncope +3, absence of urticaria/pruritus/angioedema +1, basal serum tryptase >25 ng/mL +2), the patient was referred, in accordance with current guidelines [4], to the Department of Hematology (Medical University of Vienna) for evaluation of a potential clonal mast cell disorder. No abnormalities were observed on abdominal ultrasound, chest x-ray, or dual-energy x-ray absorptiometry. A bone marrow biopsy revealed discrete hypercellular marrow with dense mast cell aggregates (>15 mast cells, $CD25^+$, $CD30^+$) of approximately 10% of total cellularity and 25% spindle morphology. A locked nucleic

Figure. Prick-to-prick test with positive results for pistachio (1), cashew (2), and pink peppercorn (4) (wheal sizes of 7.6, 6.0, and 4.5 mm, respectively). Negative result for mango pulp (3), walnut (5), pecan (6), brazil nut (7), coconut (8), and yellow mustard seed (9).
Positive control with histamine solution: 5.5-mm wheal.
Negative control with sterile 0.9% sodium chloride: no wheal.

acid clamp–mediated polymerase chain reaction assay did not detect the D816V *KIT* mutation in peripheral blood or bone marrow. Other *KIT* subtype mutations were not determined, and as the basal serum tryptase level was markedly higher than 30 ng/mL, ie, not indicative of hereditary α tryptasemia, a further diagnostic work-up for this condition was not considered necessary. A dermatological examination revealed no lesions suggestive of mastocytosis. Considering the increased baseline serum tryptase levels, the multifocal dense infiltrates of mast cells in the bone marrow (see above), and the lack of B- and C-findings, the patient was diagnosed with bone marrow mastocytosis by the Department of Hematology [4]. Given the patient's new high-risk profile and the unavailability of commercial specific IgE testing for PP, an oral food challenge (OFC) was scheduled to rule out cross-reactivity between PP and pistachio and cashew. After obtaining written and oral consent, we performed the OFC with exponential dose increments every 40 minutes, starting with 1 peppercorn and increasing to 2, 4, and 8 peppercorns, up to a total of 15 peppercorns. The patient did not experience anaphylactic reaction following the OFC. Therefore, he does not need to avoid PP as a potential allergen in the future and only received an allergy passport for cashew and pistachio, based on the high diagnostic value of Ana o 3–specific IgE [5] and notable cross-reactivity between pistachio and cashew [6]. Furthermore, there was no need for mango avoidance, given that he tolerated mango well after the anaphylactic event. However, the patient was informed about the possible risk of cross-contamination with mango seed components in industrially processed mango puree.

To our knowledge, this is the first report of an OFC with PP in a pistachio-allergic patient. Only 3 cases of anaphylaxis after PP consumption in cashew-sensitized individuals have been reported to date [7,8]. Furthermore, in none of them was an underlying mast cell disorder evaluated. Cross-sensitization of PP was evaluated by Too et al [9] with SPT in 21 nonexposed cashew- and/or pistachio-allergic individuals, revealing 76.2% cross-sensitization to PP. In their in vitro study of 56 children with suspected cashew nut allergy, Bastiaan-Net et al [3] found that 7/56 showed serological cross-sensitization for multiple Anacardiaceae species including PP. Moreover, in vitro analysis revealed that putative 2S albumin and 11S legumin storage globulin proteins cross-reacted with the serum of PP- and cashew nut–sensitized individuals. The clinical relevance of these findings was not established, and avoidance of the Anacardiaceae family was recommended. According to current EAACI guidelines on the diagnosis of IgE-mediated food allergy [10], OFCs should be performed to confirm or exclude food allergy in equivocal cases, depending on diagnostic accuracy. Furthermore, for hidden or uncommon allergens, ruling out food allergy in high-risk patients is crucial to prevent anaphylaxis, ensure accurate diagnosis and management, and improve patients' safety and quality of life. Given the unavailability of specific IgE testing for PP and subsequent equivocality in the present case, an OFC was performed without complications, despite the finding of positive sIgE for Ana o 3. However, the patient received an allergy pass for pistachio and cashew owing to the high diagnostic value of Ana o 3–specific IgE [5] and high cross-reactivity between pistachio and cashew [6], although he did not subsequently need to avoid PP.

In conclusion, the present case report highlights the safety of OFC with PP and underscores the low allergenic potential of this food, despite positive PTPT results, even in a high-risk pistachio-allergic patient sensitized to Ana o 3. However, further in vitro and in vivo studies, including standardized double-blind placebo-controlled food challenge, are essential to comprehensively determine the allergenicity of PP in at-risk individuals. Notwithstanding, genuinely allergic patients should be duly informed about cross-reactivity within the Anacardiaceae family, and food manufacturers should ensure accurate food labeling.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

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