

Adverse reaction to pomegranate ingestion

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We present a non-atopic 85-year-old woman, with a late-onset recidivant tongue angioedema due to pomegranate intake, as proven by a double blind oral challenge test. This is the first case ever reported about adverse reaction to pomegranate. We have been unable to demonstrate an IgE-mediated mechanism (prick test, histamine release test and RAST with pomegranate were all negative). We emphasize the importance of clinical history and oral challenge test in the diagnosis of food allergy.

Key words: adverse reactions to foods; angioedema; fruits; oral challenge test; pomegranate.

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Pomegranate (*Punica granatum*) is the fruit of the pomegranate tree, a dicotyledon angiosperm plant of the Punicaceae family, originally from Persia, Khurdistan and Afghanistan, from where it was brought to the Mediterranean countries by the Phoenicians, and spread from there by Romans and Arabs. The tree flowers in May-June, and its fruits mature in September-October. It is not botanically related to any other fruit for human consumption.

Few data exist about adverse reactions to pomegranate. In 1987, Ghadirian (7) reported on the possible role of pomegranate (crushed mixture of sour pomegranate seeds, black pepper, dried raisins and, occasionally, garlic) in the development of esophageal carcinoma, due to its local erosive or irritant action.

The aim of the present study is to report the first adverse reaction following pomegranate ingestion.

CASE REPORT

An 85-year-old white woman was admitted to the hospital because of tongue swelling lasting 1 h and no other symptoms.

The patient had been asymptomatic until 1 week before, when she came to our emergency room showing the same symptoms; 40 mg of methylprednisolone were administered i.m. and she improved. She was discharged on hydroxyzine, 25 mg b.i.d.

Past medical history included long-standing hypertension treated with clopamide, osteoarthritis of the hips, and cataract. She had no family or personal history of atopy.

At the time of admission, the clinical examination revealed macroglossia with enlarged papillae. White blood cell count was 6,260/ml with 169 eosinophils/ml. Her hemoglobin, urinalysis and serum chemistries (including SGOT and SGPT) were normal. Serum IgM, IgG and IgA levels were normal, as were CH50 and serum C4, C3 and C1INH levels. Chest X-ray showed scoliosis and lipomatosis. The electrocardiogram was normal. Biopsy of a tongue sample showed chronic infiltration in the chorion and groups of neutrophils in epithelium.

The patient improved when treated with hydroxyzine, 25 mg t.i.d., and was discharged 7 days after admission with a diagnosis of recidivant idiopathic tongue angioedema.

One month later she returned because of tongue swelling, which responded to methylprednisolone, but with no other clinical changes. After more detailed questioning, the patient stated that all three tongue swelling episodes had occurred a few hours after eating pomegranate. She had eaten this fruit for years without problem, but had not eaten it since the last episode. She tolerated other foods without problems.

We performed a skin prick test with pomegranate following the prick-prick method (5); the test was examined at 15 min, 6 and 24 h and the result was negative. Previously, we have proved the absence of irritant effect of pomegranate in atopic and non-atopic controls. A battery of commercially available common inhalant and food allergens were also tested (Bencard, Worthing, UK) with negative result.

Further, we performed an *in vitro* study. Pomegranate seeds were crushed to obtain a juice that was filtered and centrifugated; the obtained supernatant was dialysed. The protein content of this extract was 0.45 mg/ml (Bio Rad, München, Germany).

Total IgE was measured by IgE EIA technique according to the manufacturer's instruction (Pharmacia, Uppsala, Sweden); the result was 7 IU/ml (4.8–160 IU/ml).

Using different concentrations of pomegranate extract, a histamine release test with the automated fluorometric method of Siraganian (12) with modifications (10) showed negative.

We measured specific IgE against pomegranate following the RAST technique using our own pomegranate discs, obtained by incubating nitrocellulose paper discs with the pomegranate extract. The result was negative and similar to the control group (atopics and non-atopics).

Finally, to demonstrate a relationship between the symptom described and the pomegranate intake, we performed an oral challenge test with fresh pomegranate seeds mixed with placebo in a double blind procedure. Strawberry yoghurt was used as placebo; the pomegranate seeds were carefully crushed and mixed with 100 cl of yoghurt 10 min before challenge. The appearance and taste of the strawberry yoghurt and that mixed with pomegranate were similar;

two non-atopic controls could not distinguish between the two preparations. A single dose was given daily in the morning, and the dose was increased 2-fold in the subsequent days. The patient remained under medical supervision for 6 h after pomegranate intake. The challenge was negative to placebo but positive to ingestion of 40 g of pomegranate seeds mixed with placebo, tongue angioedema developing 4 h after, which improved after administration of steroids.

DISCUSSION

Urticaria and angioedema have been called "a vexing problem" (11). Angioedema may occur either alone (11%) or in association with urticaria (49%) (2). Non-hereditary angioedema can be associated with many different causes. According to Czarnetski (3), drugs, foods and food additives are the most usual allergic or pseudoallergic stimuli for angioedema, followed by inhalation antigens and histamine releasers.

Our case was initially diagnosed as "recidivant idiopathic angioedema" after ruling out the known causes. After detailed questioning of the patient, a fruit (pomegranate) allergy was suspected. Due to lack of data about allergic reactions in the literature, subsequent evaluation was based on two major criteria when diagnosing an adverse reaction to food: 1) verification of the relationship between symptoms and food ingestion, and 2) determination of whether the mechanism was immunological.

The oral challenge test (double blind) confirmed the diagnosis of recidivant angioedema due to pomegranate intake.

An IgE-mediated hypersensitivity could not be sustained in our patient. The history was atypical, and the *in vitro* test (histamine release and specific IgE against pomegranate) were negative. The skin test was also negative; we used the "prick-prick method" (5) using fresh fruit, a simple and sensitive method generally used in Europe when standard extracts are not available (4).

The biopsy showed no signs of vasculitis and no evidence of other immunological mechanisms. Groups of neutrophils in epithelium are a relatively common finding in tongue biopsies,

and is without pathological consequence. Biopsy was consistent with angioedema; edema is often difficult to detect because the serum in the tissues does not stain (1).

Diagnosis of food hypersensitivity can be affected by the patient's age, the pattern of putative food-allergen, and differences in the frequency of sensitivities related to local dietary habits. Spain is a major pomegranate producer, particularly in the south, and approximately 10,400 to 22,000 tons are exported, mainly to the UK, Italy and France (8).

The pomegranate tree contains several alkaloids, mainly in the root cortex in a proportion of 0.3–0.7%, and has up to 25% tannic compounds. Cortex activity is preserved for many years and is the most important medicinal component, e.g. as a vermicide (6). The seeds comprise water, glucose, citric acid, malic acid and large quantities of vitamin C (6). In 1988, Moneam reported that pomegranate contained oestrogen (1.09 mg in 100 g) but did not establish its role in the adverse reactions to this fruit (9). The present case is a recidivant angioedema caused by a late adverse reaction (intolerance) to pomegranate in which no immunological mechanism could be shown. The mechanisms governing adverse reactions to food are complex and the current diagnostic test unreliable. Thus the only test providing information about prophylactic measures necessary to avoid future reactions is the "challenge-with-suspected-agent" test.

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