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Immediate hypersensitivity reaction with mango

Natychmiastowa reakcja nadwrażliwości na mango

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Abstract

Hypersensitivity to the fruit mango is extremely rare and can exhibit either as immediate or delayed reactions. Since 1939, only 22 patients (10 with immediate type I reactions and 12 with delayed) have been documented with allergy to mango. History of atopy and geographical region may influence the type of reaction. Immediate reactions occured most often in patients with history of atopy, while delayed reactions developed in non-atopic individuals. Clustering of delayed hypersensitivity reports from Australia and immediate reactions from Europe has been documented. We report a 50-year-old man with immediate type I hypersensitivity to mango, who developed cough, wheezing dyspnoea, generalised itching and abdominal discomfort after ingestion of mango. Life threatening event can also happen making it imperative to diagnose on time, so as to prevent significant morbidity and potential mortality.

Key words: allergy, anaphylaxis, bronchial asthma, contact dermatitis, mango, urticaria

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Streszczenie

Nadwrażliwość na owoce mango jest bardzo rzadkim zjawiskiem i może przebiegać zarówno jako reakcja natychmiastowa, jak i opóźniona. Od 1939 roku udokumentowano alergię na mango tylko u 22 pacjentów (u 10 z reakcjami typu natychmiastowego i u 12 z reakcją opóźnioną). Wydaje się, że wywiad atopowy oraz region geograficzny mogą wpływać na rodzaj reakcji. Natychmiastowe reakcje obserwowano najczęściej u pacjentów z wywiadem atopii, natomiast reakcje opóźnione byłych częstsze u pacjentów bez takiego wywiadu. Dane epidemiologiczne wskazują, że na terenie Australii dominuje nadwrażliwość z opóźnionym typem reakcji, w Europie zaś przeważają reakcje typu natychmiastowego.

W pracy przedstawiono przypadek 50-letniego mężczyzny z nadwrażliwością typu I natychmiastowego na alergeny owocu mango, u którego po spożyciu mango wystąpił kaszel, świszczący oddech i duszność, uogólniony świąd skóry i dolegliwości brzuszne.

Diagnostyka w takich sytuacjach powinna być przeprowadzona możliwie szybko, aby wdrożyć wtórną profilaktykę, uniknąć ekspozycji i zapobiegać stanom zagrażającym życiu w przebiegu nadwrażliwości.

Słowa kluczowe: allergy, anaphylaxis, bronchial asthma, contact dermatitis, mango, urticaria

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Introduction

The fruit mango (*Mangifera indica*), often known as the 'king of fruits', belongs to the family *Anacardiacae*. During the summer months, India produces nearly half of the mangoes cultivated throughout the world and is the national fruit of the country. Despite being consumed in large quantities and in many forms in our country, hypersensitivity reactions to mango are extremely rare. Hypersensitivity to the fruit mango can manifest in two forms, immediate and delayed. To

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date, there are only 22 patients with documented hypersensitivity to mango. Of these 22 patients, 10 [1–9] exhibited immediate hypersensitivity while 12 [10–17] had delayed hypersensitivity reactions. Of the 10 patients with immediate hypersensitivity, two were reported from India [6, 9]. The mango allergen is known to cross react with *Artemisia* pollen, birch pollen, poison ivy, carrot, celery, pistachio nut, banana, tomato and papaya [8]. Paucity of the literature on the subject prompted this report of the 50-year-old man with immediate hypersensitivity reaction in the form of wheezing dyspnoea, generalised itching and abdominal discomfort after ingestion of fresh mango.

Case report

A 50-year-old male office worker, a never-smoker, was referred to our Institute for evaluation of hypersensitivity to the fruit mango. He had wheezing dyspnoea and cough for 10 years which initially were episodic but had recently become troublesome. These complaints were preceded by nasal symptoms which had commenced about 15 years ago in the form of paroxysmal sneezing, rhinorrhoea and nasal itching. Nasal blockage and post nasal drip too occurred off and on. All respiratory symptoms aggravated during change of season and whenever he ingested mango during the mango season. This also caused skin allergy which manifested as itching and rashes. Symptomatic treatment and avoidance of mangoes for past 10 years had partially controlled his symptoms.

Physical examination revealed a middle aged man in no acute distress.There was no pallor, icterus, clubbing, cyanosis or pedal oedema. Oxygen saturation at room air was 98%. Diaphragmatic excursion was equal on both sides. On auscultation, vesicular breath sounds along with bilateral polyphonic expiratory rhonchi were audible over all lung fields. Nasal mucosa was erythematous.

Complete blood counts revealed a total leucocyte count of 9900 cells per cubic millimeter with an eosinophil count of 10.8%. Absolute eosinophil count was 1000 cells per cubic millimeter. Serum total Ig E value was 358 kUA/L (reference range < 64.00). Specific IgE against mango was 1.38 kUA/L (Immunocap [100] system) suggesting presence of moderate levels of mango specific antibodies. Renal as well as hepatic functions were within normal limits. The chest radiograph revealed no abnormalities but a non-contrast CT scan of the paranasal sinuses showed bilateral maxillary, bilateral ethmoidal and left sphenoidal sinusitis. Pulmonary function testing showed a ratio of FEV_1/FVC of 62% with a FVC of 3.99 L (126% of predicted), an FEV_1 of 2.48 L (95% of predicted) but there was no significant increase in FEV_1 after inhalation of 400 micrograms of salbutamol. This was suggestive of an obstructive pattern with mild airflow limitation. Neither was there any significant reversibility nor did the peak flow diary reveal any circadian variation.

Skin prick testing with the battery of standard aeroallergens demonstrated immediate hypersensitivity to weeds (*Ageratum*, *Amaranthus spinosus*, *Argemone*, *Artemisia*, *Gynandropsis* and *Parthenium*). Prick to prick testing from a fresh ripe mango was done along with a negative control (buffered normal saline [1 × 1 mm]) and a positive control (histamine [6 × 6 mm]). This elicited an immediate type I hypersensitivity reaction to the mango extract (14 × 10 mm).

A week later, the patient agreed to ingest a small slice of fresh mango under observation in the emergency room. After an informed consent was taken, he was examined prior to ingestion of mango and spirometry and peak flow rates were also recorded. Oxygen saturation at room air was 98%. Within 5 minutes of ingestion of mango, he complained of itching in the oral cavity. Generalised itching and abdominal discomfort too commenced which peaked after 1 hour. This was followed by a bout of coughing, audible wheezing dyspnoea and throat irritation. Polyphonic rhonchi were audible over all lung fields. The peak flow rate fell from 4.10 L/min to 2.92 L/min, a decrease of 1180 mL (28%). The spO_2 fell to 93% at room air and FEV_1 fell from 3.3 L to 2.67 L. These manifestations subsided within half an hour after injectable adrenaline, pheniramine and dexamethasone along with nebulisation with salbutamol, ipratropium and budesonide. After 2 hours of mango ingestion, he vomited mango remnants (Table 1).

A diagnosis of bronchial asthma and allergic rhinitis along with immediate hypersensitivity to the fruit mango was made and the patient was strongly advised not to ingest mango in any form. He was also initiated on a combination of inhaled budesonide and formoterol along with mometasone nasal spray. This was done as soon as the diagnosis was established. With this, the patient experienced significant relief and his symptoms were minimised on maintenance therapy.

Table 1. Mango ingestion provocation test

Time	Clinical profile	spO_2	PFR (L/min)	FEV_1 (L)
Pre-mango ingestion	No symptoms with normal vesicular breathing	98%	410	3.3
5 minutes	Itching in oral cavity	98%	420	–
15 minutes	Generalised itching and abdominal discomfort	98%	410	–
30 minutes	Increasing generalised itching and abdominal discomfort	98%	410	–
45 minutes	Further aggravation of generalised itching and abdominal discomfort	97%	400	–
60 minutes	Generalised itching and abdominal discomfort accompanied by throat irritation, bout of coughing, audible wheezing dyspnoea and polyphonic rhonchi	95%	290	–
70 minutes	Aggravation of all symptoms including generalised itching and abdominal discomfort, throat irritation, coughing, wheezing dyspnoea, polyphonic rhonchi	93%	200	2.67
Post-treatment 15 minutes	↓ itching, ↓cough and wheezing dyspnoea, ↓ rhonchi	96%	320	–
Post-treatment 30 minutes	↓cough and wheezing dyspnoea, ↓ rhonchi	96%	360	–
Post-treatment 60 minutes	Vomiting containing mango remnants, no cough, wheezing dyspnoea or rhonchi	98%	400	–

Discussion

Mango is native to southern Asia and has been cultivated in the Indian subcontinent for thousands of years. It is consumed in various forms both during the season as well as off season. During season, it is partaken in form of fresh fruits, shakes and ice creams while during off season, it is cherished as pickles, jams and juices. Immediate hypersensitivity can manifest as anaphylaxis, angioedema, erythema, urticaria, wheezing dyspnoea while delayed reaction as contact dermatitis, oral allergy syndrome and periorbital oedema [18].

A recent review [18] presented 22 patients with documented hypersensitivity to the fruit mango, 10 of whom had immediate hypersensitivity, while 12 presented with delayed hypersensitivity reactions with predominant skin manifestations. The first report of an allergic reaction to mango was a description of delayed hypersensitivity manifestation from USA in 1939 by Zakon [10]. The report described a young female who developed acute vesicular dermatitis involving lips and circumoral area, 24 hours after ingestion of mango. The first case of immediate hypersensitivity too was reported from USA by Kahn [1] in 1942. The patient developed hoarseness, dyspnoea and wheezing within 30 minutes of mango ingestion. These symptoms were relieved with injectable epinephrine. Our patient too, a case of immediate hypersensitivity type I reaction to mango, experienced bout of coughing, wheezing dyspnoea, throat irritation within 1 hour of mango ingestion.

Of the ten patients documented with immediate reaction to mango, erythema developed in three [3–4, 7], angioedema in five [2, 4, 6–8], respiratory distress/dyspnea in nine [1–9] and anaphylaxis in two patients [2, 3], one of whom had a life threatening anaphylactic shock [2]. Symptoms in most of these patients occurred almost immediately [3–9], while in two patients, symptoms commenced in around 30 minutes [1, 2]. History of atopy, also present in our patient, was available in eight others [1, 2, 4, 5, 7–9].

Skin prick tests and immunoassays of serum food specific IgE levels can detect the allergen specific IgE. These tests are only supportive and can aid in the diagnosis but it is imperative that it be performed in light of an appropriate clinical history. In IgE mediated food allergy, the wheal size correlates with the likelihood of clinical allergy. However, wheal size can be highly variable as it depends on age, diurnal variation and site on the body where SPT is performed. The individual's skin reactivity as well as the SPT device and reagents used also play a role [19].

The ICON statement on "Food Allergy" [19] issued jointly by the American Academy of Allergy, Asthma and Immunology; European Academy of Allergy and Clinical Immunology; World Al-

lergy Organization; and the American College of Allergy, Asthma & Immunology has stressed the need for studies to define the diagnostic accuracy of 95% positive predictive value wheal sizes for different foods, ages, diseases, and populations. Information regarding the skin allergy test to mango was available in eight of the ten patients with immediate hypersensitivity to mango and was positive in all [2, 4, 5, 6–9]. Our patient too had a skin prick test positive to mango extract.

Food specific IgE is also often used for establishing the diagnosis of food allergy but has the same status as skin prick testing [19]. Specific IgE against mango was evaluated in six patients [4–8], but was positive in only three [5, 6, 8]. In our patient too, specific IgE against mango antigens was detected in moderate levels. The possible explanation behind the under detection of specific IgE may be the unstability of the corresponding allergens, which remain undetected and also the current IgE detection system appears to lack some of the specific mango allergens [18]. Combining skin prick testing results with serum food specific IgE may be of value in diagnosing food allergy [20]. Wheal size with skin prick testing and serum food specific IgE levels correspond with the plausibility of clinical allergy but it must be highlighted that they do not correlate with or predict the severity of allergic reaction to a food [19].

Although, the double-blind, placebo-controlled food challenge (DBPCFC) remains the gold standard for the diagnosis of food allergy, it is less frequently performed as it requires time, huge resources and appropriate set-up. In clinical practice, single blind or open food challenges are generally performed, though DBPCFC is the most specific test to confirm food allergy. There is a risk of immediate allergy and anaphylaxis, so it is essential that food challenge should always be performed in a well equipped facility under medical supervision with appropriate medications and resources available for emergency management of anaphylaxis [19].

Immediate hypersensitivity is a classical IgE mediated reaction and usually occurs in individuals who are previously sensitised to mango antigens [5]. Sensitisation may occur by prior mango ingestion or by intake of other fruits belonging to *Anacardiaceae* family. Even unrecognisable forms such as fruit punch can also sensitise the patient [2]. Allergenicity of mango nectar persists even after heating, enzymatic degradation and mechanically caused tissue degradation as evidenced by allergic reaction to canned or packaged mango [21].

Mango antigen also cross-reacts with *artemisia* pollen, birch pollen, poison ivy, mugwort, celery, carrot, pistachio nut, tomato, papaya and banana [10]. Mostly, Bet v1, Bet v6, and Art v1 related allergens lead to cross-reactions between mango and other plants and fruits [7]. A study has documented that the common epitopes are shared by allergens from mango fruit and allergens from birch pollen, mugwort pollen, celery, and carrot [22]. Mango allergy was also seen in individuals with latex hypersensitivity [7, 23]. The possible explanation is that multiple antigens can bind to an IgE antibody at corresponding sites, thus mediating an immune response. Allergens, termed as profilins, responsible for cross reactivities between botanically unrelated pollens and fruits can account for this phenomenon [22]. However, this has yet to be proved conclusively.

The first case of delayed hypersensitivity to mango was reported in 1939 in USA. Subsequent reports are from Asia, Australia and North America. Amongst the twelve such patients documented in the literature so far [10–17], urticaria was present in eight [10–13, 15], oral allergy syndrome in two [1, 17] and periorbital edema in two [13, 15]. Three of these patients [10, 13, 15] developed the symptoms after mango ingestion, while in the remaining nine patients, the reaction occurred after contact with mango skin or bark of mango tree [11, 12, 14, 16, 17]. Duration of onset of symptoms was variable and ranged from 4 hours [11] to 7 days [12]. Patch testing, done in ten patients [11, 13–17], was positive in all. Cross reactivity was not reported in any patient nor was there any information regarding specific IgE antibody against mango antigen in any of the twelve patients.

Delayed hypersensitivity reaction to mango is cell mediated and was seen mainly in form of contact dermatitis, oral allergy syndrome and periorbital oedema. Direct contact with the mango or tree itself and ingestion too, can lead to a cell mediated reaction. Sensitising substances present in the skin, bark, pericarp as well as the mango pulp up to five millimeters below the skin include uroshiol, cardol, limonene and B-pinene [18].

Since 8 of the 10 patients with immediate type I hypersensitivity reactions had a history of atopy, it appears that atopy may be a risk factor for a type I reaction with mango. In contrast, in patients with delayed manifestations, history of atopy was seen in only one of 12 documented patients, suggesting that delayed hypersensitivity occurs in non-atopic subjects.

Further, geographical region may influence the type of reaction. There are five reports of

Table 2. Documented reports of hypersensitivity to mango from Australia

Age, Sex, Year, Country, Reference	Geographical region cultivating the fruit	Type of reaction	History of atopy	Presenting symptoms after mango ingestion	Time of onset of symptoms	Treatment received	SPT to mango extract	Patch testing to mango extract	Cross reactivity	Specific IgE against mango	Symptoms after mango ingestion provocation test
21, female, 1995, Australia [11]	Yes	Delayed hypersensitivity	No	Intensely pruritic linear papulo-vesicular lesions on lower legs, urticarial plaques on forearms (contact dermatitis)	4 hours	NA	NA	Positive	NA	NA	NA
31, female, 1995, Australia [11]	Yes	Delayed hypersensitivity	No	Intensely pruritic confluent urticaria over arms and abdomen (contact dermatitis)	12 hours	NA	NA	Positive	NA	NA	NA
27, female, 1995, Australia [11]	Yes	Delayed hypersensitivity	No	Pruritic confluent urticaria on neck, acute eczematous plaques with bullae on arms (contact dermatitis)	6 days	NA	NA	Positive	NA	NA	NA
36, male, 1995, Australia [11]	Yes	Delayed hypersensitivity	No	Widespread acute eczematous and urticarial plaques (contact dermatitis)	5 hours	NA	NA	Positive	NA	NA	NA
42, female, 2008, Australia [16]	Yes	Delayed hypersensitivity	No	Itchy palpable, pruritic lesions over arms, legs, neck and abdomen (contact dermatitis)	4 days	Prolonged treatment with topical steroids	NA	Positive to mango	NA	NA	NA

IgE — immunoglobulin E; NA — not available; SPT — skin prick test

Table 3. Documented reports of hypersensitivity from Europe

Age, Sex, Year, Country, Reference	Geographical region cultivating the fruit	Type of reaction	History of atopy	Presenting symptoms after mango ingestion	Time of onset of symptoms	Treatment received	SPT to mango extract	Patch testing to mango extract	Cross reactivity	Specific IgE against mango	Symptoms after mango ingestion provocation test
32, male, 1988, UK [4]	No	Immediate hypersensitivity	Positive	Periorbital edema, facial erythema, diffuse urticaria, dyspnoea	20 minutes	Inj. epinephrine and inj. hydrocortisone	Positive	NA	NA	Negative by RAST	NA
45, female, 1999, Spain [5]	Yes	Immediate hypersensitivity	Positive, latex sensitivity present	Rhino–conjunctivitis, oral allergy, cough, dyspnoea	Immediately	Antihistamines and corticosteroids	Positive	Not done	Positive for latex	Raised by RAST	NA
46, female, 2008, Germany [7]	No	Immediate hypersensitivity	Positive	Sneezing, rhinorrhoea, dyspnoea, dysphagia, anxiety	< 10 minutes	NA	Positive	NA	Positive for ginger and pistachio	Negative	NA
24, male, 2008, Germany [7]	No	Immediate hypersensitivity	Received immunotherapy for mugwort sensitization	Urticaria, swelling of face and hands	10 minutes	NA	Positive	NA	Positive for mugwort, pistachio and ragweed	Negative	NA
39, female, 2009, Spain [8]	Yes	Immediate hypersensitivity	Positive	Facial angioedema, hoarseness, pruritis of palms, respiratory distress (oral allergy syndrome)	Immediately	Inj. epinephrine and corticosteroids	Positive	Not done	Positive to Artemesia pollen and house dust mites	Positive	NA

IgE — immunoglobulin E; NA — not available; RAST — radio allergo sorbet assay; SPT — skin prick test

Table 4. Documented reports of hypersensitivity to mango from Asia

Age, Sex, Year, Country, Reference	Geographical region cultivating the fruit	Type of reaction	History of atopy	Presenting symptoms after mango ingestion	Time of onset of symptoms	Treatment received	SPT to mango extract	Patch testing to mango extract	Cross reactivity	Specific IgE against mango	Symptoms after mango ingestion provocation test
NA (2 patients), 2004, Japan [14]	No	Delayed hypersensitivity	No	History of mango dermatitis present (contact dermatitis)	NA	NA	NA	Positive to mango extract	Positive for uroshiol	NA	NA
43, female, 2007, India [6]	Yes	Immediate hypersensitivity	Negative	Oropharyngeal itching, angioedema of face, respiratory distress	< 10 minutes	Inj. hydrocortisone and antihistamines	Positive	Not done	Positive for Indian dill, cashew apple, Anethum, Anacardium	Positive by ELISA and SDS–PAGE	NA
42, female, 2008, Thailand [15]	Yes	Delayed hypersensitivity	No	Patchy pruritic erythema of the face, and extremities with periorbital edema (contact dermatitis)	1 day	S/S subsided after 5 days with oral prednisolone and chlorpheniramine	NA	Positive to mango extract	NA	NA	NA
27, female, 2009, Korea [17]	No	Delayed hypersensitivity	No	Eczematous rash and blister formation around lips (oral allergy syndrome)	NA	NA	NA	Positive to mango	NA	NA	NA
46, female, 2011, India [9]	Yes	Immediate hypersensitivity	Positive	Wheezing dyspnoea, paroxysmal cough, throat irritation	15 minutes	Nebulization with albuterol and ipratropium	Positive	Not done	NA	NA	Immediate bout of coughing, dyspnoea, throat irritation. Fall in PFR of 490 ml. (9%) 30 min later
*50, male, 2013, India	Yes	Immediate hypersensitivity	Positive	Oropharyngeal itching, throat irritation, itching and erythema over body, abdominal discomfort, wheezing dyspnoea, paroxysmal cough	10 minutes	Nebulisation with salbutamol and ipratropium, inj. hydrocortisone and inj. pheniramine	Positive	Not done	Positive for Ageratum, Amaranthus Spinosus, Argemone, Artemisia, Gynandropsis, Parthenium	1.38 kUA/L (moderate) by Immunocap [100] system	Oropharyngeal itching, throat irritation, wheezing dyspnoea, cough. Fall in PFR of 1180 ml. (28%) 1 hour later

*current report; ELISA — enzyme linked immunosorbent assay; IgE — immunoglobulin E; NA — not available; PFR — peak flow rate; SDS PAGE — sodium dodecyl sulphate polyacrylamide gel electrophoresis; SPT — skin prick test

Table 5. Documented reports of hypersensitivity to mango from North America

Age, Sex, Year, Country, Reference	Geographical region cultivating the fruit	Type of reaction	History of atopy	Presenting symptoms after mango ingestion	Time of onset of symptoms	Treatment received	SPT to mango extract	Patch testing to mango extract	Cross reactivity	Specific IgE against mango	Symptoms after mango ingestion provocation test
29, female, 1939, USA [10]	No	Delayed hypersensitivity	NA	Itching and vesicular lesions in circumoral region, swelling of lips (oral allergy syndrome)	24 hours	NA	NA	NA	NA	NA	NA
NA, female, 1942, USA [1]	No	Immediate hypersensitivity	Positive	Hoarseness, dyspnoea and wheezing	30 minutes	Inj. epinephrine	NA	NA	NA	NA	Rapidly acute symptoms of hoarseness and wheezing
32, male, 1965, USA [2]	No	Immediate hypersensitivity	Positive	Itching of eyes, lacrimation, swelling of eyelids, chest tightness, noisy breathing	30 minutes	Inj. epinephrine and inj. hydrocortisone	Positive passive transfer reaction	NA	Positive to house dust, almond, wheat, watermelon	NA	NA
24, female, 1967, USA [3]	No	Immediate hypersensitivity	Negative	Gasping for breath, erythema, swelling of face and extremities, hypotension and shock	10 minutes	Inj. dexamethasone and inj. epinephrine	NA	NA	NA	NA	NA
27, male, 1998, USA [12]	No	Delayed hypersensitivity	Sensitivity to poison oak and poison ivy	Pruritic and eczematous rash (contact dermatitis)	7 days	Resolved after a week's treatment with topical steroids	NA	NA	NA	NA	NA
22, female, 2004, USA [13]	No	Delayed hypersensitivity	No	Patchy pruritic erythema of face, neck and arms with periorbital edema. Papular lesions extended to chest, upper extremities. (contact dermatitis)	2 days	S/S subsided after few days with oral steroids and topical fluocinonide cream	NA	Positive to mango skin, nickel and p–tert butylphenol formaldehyde	NA	NA	NA

IgE — immunoglobulin E; NA — not available; SPT — skin prick test

hypersensitivity to mango from Australia, all of whom presented with delayed hypersensitivity reaction and none had history of atopy. All these five patients had negative skin prick test for mango while patch testing was positive in all [11, 16] (Table 2). On the other hand, all five patients documented from Europe had immediate type I hypersensitivity reactions and history of atopy was present in all. All these five patients also had a positive skin prick test for mango [4, 5, 7, 8] (Table 3). Of the six patients documented from Asia, two were immediate from India while four presented with delayed hypersensitivity (two from Japan, one from Thailand and one from Korea) [14, 15, 17]. There are no reports of delayed hypersensitivity reaction from India (Table 4). Of the six patients documented from North America, all from USA, three each presented with immediate and delayed hypersensitivity (Table 5).

Both *in vitro* and the *in vivo* tests were performed in our patient to confirm the mango allergy. Skin test with extract showed wheal and flare reaction of more than histamine (positive control) indicating IgE against mango allergen bound to the mast cells were degranulated by the allergen extract. Similarly, Immuncocap results indicated the free IgE in serum of patient. In the study, skin prick testing was done with weeds to find out whether food-specific IgE antibodies were cross-reacting in nature or not. Therefore, an oral mango challenge was performed to confirm food allergy. These data proved that our patient had immediate hypersensitivity to mango.

Our report highlights the fact that hypersensitivity manifestations to mango can include both immediate and delayed reactions. Immediate reaction can also result in life threatening events. If not diagnosed on time, allergic reactions to the fruit can lead to significant morbidity and possible mortality.

Conflict of interest

The authors declare no conflict of interest.

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