Report of a Case of IgE-Mediated Anaphylaxis to Fenugreek

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Fenugreek (Trigonella foenum-graecum) is an annual plant of the Fabaceae family that is used as an herb, mainly in the Mediterranean region, southern Europe, and western Asia. The Fabaceae or Leguminosae are flowering plants commonly known as the legume and pea or bean families. Allergic reactions to fenugreek are uncommon [1,2]. Patients sensitized to the peanut allergens Ara h 1 and Ara h 3 were reported to show cross-reactivity to 7S vicilin-like and 11S legumin-like allergens in fenugreek [3].

We report the case of a 34-year-old atopic woman who presented at our university allergy department 5 months ago with a history of facial flushing, angioedema, dyspnea, nausea, vomiting, and diarrhea shortly after ingestion of a Chinese vegetable soup (Ring and Messmer, grade III). On a second occasion, ingestion of a pork sausage with mixed spices led to a similar clinical picture. She also reported atopic dermatitis and known peanut allergy that had led to severe immediate-type reactions in childhood. Allergic rhinitis due to timothy grass was currently being treated with allergen-specific immunotherapy. She also had perennial asthma, which was being treated with inhaled corticosteroids and long-acting β₂-agonists.

The result of skin prick testing (ALK-Abelló) was positive for timothy grass, mugwort, and peanut. Prick-to-prick testing with foods showed a wheal of 2 mm for pork sausage and was negative for pork and beef. Specific IgE (CAP FEIA, Thermo Fisher) was positive for Ara h 1 (3.88 kU/L), Ara h 2 (8.56 kU/L), Ara h 3 (0.36 kU/L), Art v 3 (0.75 kU/L), and fenugreek seeds (2.1 kU/L) and negative for α-gal, Tri a 19, Tri a 14, celery, pork, Bet v 1, and Art v 1. Total IgE (57.2 kU/L) and serum tryptase were within the normal range. A titrated, single-blind, placebo-controlled oral challenge test (OCT) was performed with celery (maximum single dose of 20 g, cumulative dose of 40 g), caraway (maximum single dose of 20 g, cumulative dose of 40 g), mugwort (maximum single dose of 20 g, cumulative dose of 40 g), and fenugreek (cumulative dose of 5 mg) on separate days. Celery and caraway were both ingredients in the ingested food, and a cross-reaction was suspected because of the patient’s sensitization to mugwort. While caraway was well tolerated, celery and mugwort induced oral contact urticaria and allergic rhinitis. Five

minutes after ingestion of fenugreek, the patient developed oral contact urticaria, abdominal pain, nausea, dyspnea, and generalized urticaria. The symptoms resolved completely with intramuscular epinephrine and intravenous prednisolone.

IgE-immunoblotting and mass spectrometry were used to identify and characterize potential fenugreek allergens. Fenugreek proteins were extracted from the fenugreek powder/seeds using Tris–ammonium pentaborate buffer (pH 8.7), Tris-glycine buffer (pH 8.7), and ammonium carbonate buffer (pH 7.9) and pooled. Twenty micrograms of protein was separated using 2-dimensional electrophoresis. The first dimension was performed on a Protean IEF Cell (BioRad), and the second was performed on an Invitrogen XCell Sure Lock Mini Cell system (Whatman Protran BA83). Immunodetection was performed with the patient’s serum (diluted 1:5 in PBS) and a horseradish peroxidase–labelled mouse monoclonal antibody targeting human IgE (Southern Biotechnology). SYPRO Ruby–stained protein spots were manually matched with IgE-reactive spots on the membrane, excised, and subjected to tryptic digestion and mass spectrometry, as published elsewhere [4]. They were then modified according to Spiric et al [5]. Protein Lynx Global Server version 3.03 (Waters) and the UniProt database (April 2014) restricted to entries for green plants were used for the data analysis after application of standard processing parameters.

In total, 8 proteins were identified in IgE-binding spots by mass spectrometry. These were matched with the protein sequences from other sources (Figure). A number of peptides with sequence identity to Len c 1 from lentil and Pis s 1 from peas were identified in spots 1-6, which belong to the vicilin protein family (<55% sequence identity to Ara h 1). Additionally, the proteins in the most intense IgE spots on the gel were identified as lectin and uncharacterized proteins of wheat (spot 7) and of kidney beans and moss plants (spot 8). These proteins have not been reported to be allergenic in other plants, and no clinically relevant allergy was found to any of these allergens in the present case.

Additionally, the patient’s serum showed IgE binding to major peanut allergens on 1D immunoblot for Ara h 1, Ara h 3, Ara h 2, and Ara h 6 (data not shown, although the peptide homologues were absent in the fenugreek extract).

Sequencing the fenugreek genome in combination with proteomic analysis of fenugreek extract would enable better identification of the culprit proteins responsible for the allergic reaction, since in most reported cases, fenugreek allergens from cross-reactions to peanut allergens were not identified, and cross-reactivity to other legumes such as soy and lupin has also been demonstrated [6-8]. Cross-reactivity to the lipid transfer protein of mugwort (Art v 3) and celery is also possible, although the clinical reaction to celery and mugwort in the challenge was clearly less intense than to fenugreek.

The low-molecular-weight range proteins in fenugreek extract appear to be more relevant in the present case owing to the fact that the IgE-binding reactivity observed was more pronounced than with the high-molecular-weight proteins. Therefore, further studies on optimization of extraction would be beneficial for more precise identification of culprit proteins.

Unfortunately, the patient was lost to follow-up and not available for further investigations, such as cross-inhibition testing.

In summary, we present a rare case of anaphylactic reaction to fenugreek due to unknown allergens.

Fenugreek is used as an ingredient not only in mixed spices, but also in natural remedies, artificial maple syrup, coffee substitute, cheese, and supplement in baked goods [9]. In Europe, fenugreek does not have to be declared, thus making avoidance very difficult and challenging for patients whose primary allergy is to peanut [10].

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**Conflicts of Interest**

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**References**

Acute Eosinophilic Pneumonia Induced by Varnish Particles: A Diagnostic Challenge

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Acute eosinophilic pneumonia (AEP) is a rare disease of unknown cause. Unlike chronic idiopathic eosinophilic pneumonia, the disease mostly affects males with no history of asthma or allergies [1]. Several types of exposure, such as a recent change in tobacco consumption, are thought to be responsible for AEP [2]. Given that the clinical presentation of AEP is nonspecific (cough, fever, pleural effusion), the condition can often be mistaken for acute infectious pneumonia or acute respiratory distress syndrome (ARDS) [3]. The key investigation is bronchoalveolar lavage (BAL), which confirms AEP by revealing an eosinophilic cell pattern (>25% eosinophils) in the differential cell count of BAL fluid. We report a case of AEP induced by domestic exposure to varnish particles and illustrate the difficulty in diagnosing this condition correctly.

A 57-year-old man with no medical history of interest presented to the emergency department with a 2-day history of chest pain, dry cough, and progressive dyspnea. He had no history of smoking, substance use, or allergy. He was in excellent physical condition and exercised every day. Ten days before his first respiratory symptoms, he had been exposed for several days to varnish particles without respiratory protection in a confined environment (wooden door maintenance). Twenty-four hours before admission, his family doctor had prescribed prednisone for flu-like syndrome.

On examination in the emergency department, he was febrile with dyspnea at rest and oxygen saturation of 87% in ambient air. Auscultation revealed bilateral bronchial sounds with crackles. Thoracic computed tomography (CT) revealed interstitial syndrome (interlobular septal thickening) and bilateral ground-glass pattern with bilateral basal condensations. Biological tests revealed inflammatory syndrome. Kidney and liver function were normal. Intravenous cefotaxime and spiramycin were initiated for suspected atypical pneumonia. On the seventh day after admission, the patient was intubated for mechanical ventilation owing to hypoxemia. A second thoracic CT scan carried out on day 8 revealed worsening of the previous abnormalities.

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