

# Recurrent Anaphylaxis Due to Lupin Flour: Primary Sensitization Through Inhalation

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## ■ Abstract

Allergic reactions to lupin have increased in parallel with the growing use of lupin flour by food manufacturers. We studied a patient with recurrent anaphylaxis to manufactured foods and a history of rhinitis-asthma related to lupin inhalation and legume tolerance. Skin prick tests with airborne and food allergens, specific immunoglobulin (Ig) E determinations, and an inhalation exposure test to ground lupin were carried out. Lupin allergens and cross-reactivity with other legumes were also studied using sodium dodecyl sulfate polyacrylamide gel electrophoresis and immunoblotting/immunoblotting inhibition.

The skin tests and specific IgE were positive for lupin and vetchling and negative for other legumes. The presence of lupin flour in the implicated foods was confirmed. Immunoblotting showed multiple IgE-binding bands (10-40 kDa) for lupin and vetchling but not for peanut, pea, or soy extracts. Immunoblotting inhibition demonstrated intense lupin-vetchling cross-reactivity.

We present a case of recurrent anaphylaxis due to lupin flour as a hidden food allergen with primary sensitization due to exposure to ground lupin via inhalation. We found cross-reactivity between lupin and vetchling but not other legumes.

**Key words:** Vetchling flour. Food allergy. Hidden allergen. Lupin flour.

## ■ Resumen

La harina de altramuz se ha introducido de forma creciente en la industria alimentaria. Paralelamente, han aumentado las reacciones alérgicas. Hemos estudiado una paciente con anafilaxia recurrente con alimentos industriales e historia en el pasado de rinitis-asma en relación con inhalación de altramuz. Toleraba otras legumbres. Se realizó prick-test con alérgenos inhalantes y alimentos, determinación de IgE-específica y exposición inhalativa a altramuz molido. Se estudiaron los alérgenos del altramuz y su reactividad cruzada con otras leguminosas (SDS-PAGE-Inmunoblot/blot-inhibición).

Las pruebas cutáneas y la IgE-específica fueron positivas a altramuz y almorta (negativas a otras leguminosas). Se confirmó la presencia de harina de altramuz en los alimentos implicados. El inmunoblot-IgE mostró múltiples bandas (10-40 KDa) en los extractos de altramuz y almorta y ninguna banda en los extractos de cacahuete, guisante y soja. La inhibición del inmunoblot demostró una intensa reactividad cruzada entre altramuz y almorta.

Presentamos un caso de anafilaxia recurrente por harina de altramuz como alérgeno alimentario oculto. La exposición inhalada en el pasado a altramuz molido fue el sensibilizante primario. Hemos encontrado reactividad cruzada entre altramuz y almorta pero no con otras leguminosas.

**Palabras clave:** Harina de almorta. Alergia alimentaria. Alérgeno oculto. Harina de altramuz.

## Introduction

The prevalence of allergic reactions to lupin (*Lupinus albus*), a member of the legume family, has increased in recent years with the growing use of lupin flour as a wheat or soy substitute in manufactured foods. Because it often appeared as an unlabeled ingredient, the substance was identified as a hidden food allergen. With the coming into force of the European food labeling Directive 2006/142/EC on December 23, 2008, however, lupin is now considered a potentially allergenic ingredient that must be specifically included by food manufacturers on their labels.

We report the case of a 54-year-old woman with a personal history of hypothyroidism and osteoporosis treated with tyrosine and estrogen replacement therapy who presented at our department on several occasions with diverse food-related allergic episodes.

In 2001, she presented generalized urticaria, lip angioedema, itching in the ears and throat, dysphonia, and cough immediately on eating lupin seeds. She avoided lupin after this episode and tolerated other legumes such as peanuts, lentils, chickpeas, green beans, white beans, peas, and soy. One year later, she ate a chocolate waffle (brand, Mildred) and immediately developed similar symptoms, in addition to hypotension. She subsequently tolerated other brands of chocolate waffles well. In 2004, she noticed itching of the mouth while eating spaghetti served with a ready-made tomato sauce (*tomate frito*;

brand, Apis). She developed no other reactions on eating other ready-made, canned, and natural tomato sauces or the same brand of spaghetti on later dates. In 2006, she developed a new episode of oropharyngeal pruritus, cough, and erythematous eruption on her face and palms after eating a chocolate cake from an unknown manufacturer. In the same year, she also developed anaphylaxis after eating a commercial ham and cheese sandwich (*San Jacobo*; brand, Rovi). She later tolerated jam, cheese, egg, bread, chocolate, and nuts (almonds, walnuts, and hazelnuts). In February 2007, she developed another anaphylactic episode after eating a chocolate waffle (brand, Dimi Dulces). None of the foods mentioned had any common ingredients listed on the labels.

She is currently free of bronchial symptoms but 15 years ago, over a 3-year period, whenever she visited her parent's home (at any time of the year), she developed itching of the eyes and nose, sneezing, watery rhinorrhea, nasal stuffiness, and cough at night. The symptoms resolved with inhaled albuterol and an antihistamine. Around that time, her mother, who had diabetes mellitus, had adopted the habit of grinding lupin seeds to use as a sweetener.

Blood count and biochemical parameters were within normal ranges. Chest x-ray and spirometry findings were also normal and the bronchodilator test was negative. Skin prick tests to inhalant allergens were positive for olive and grass pollens and negative for other pollens, house dust mites, molds, and dog and cat dander. Skin prick tests with commercial

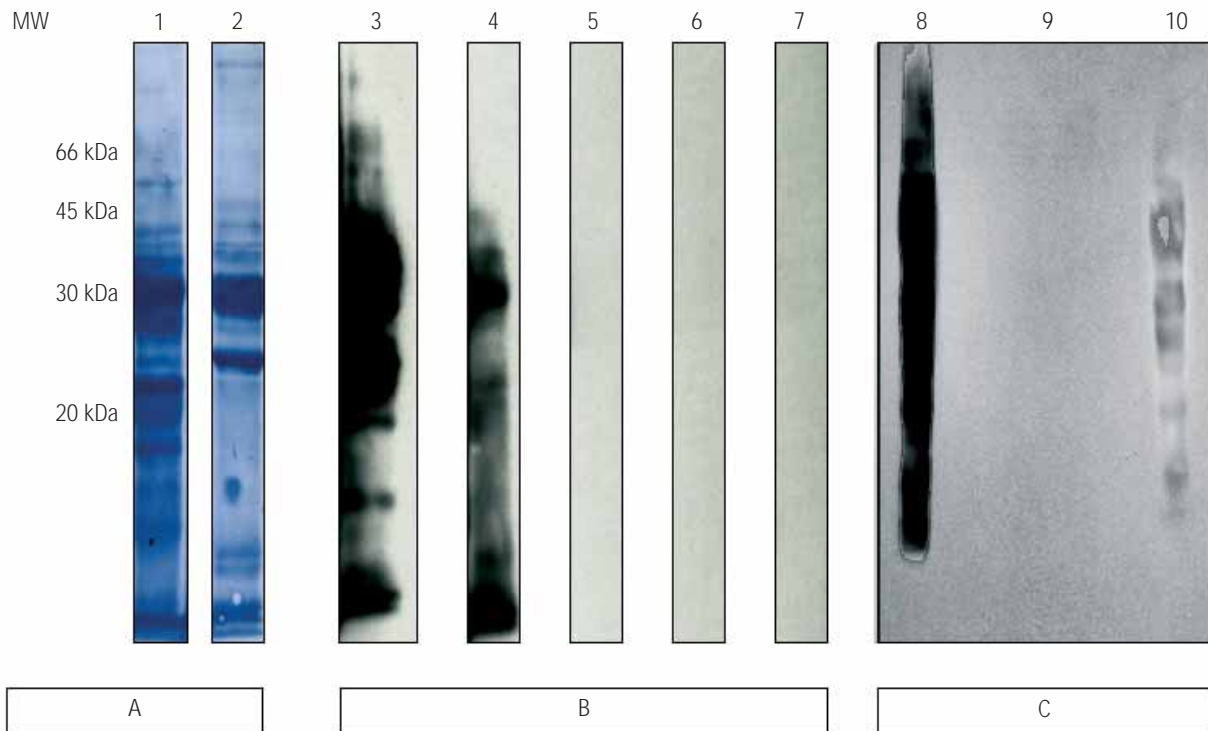


Figure 1. A, sodium dodecyl sulfate polyacrylamide gel electrophoresis. 1, lupin; 2, vetchling. MW indicates molecular weight. B, immunoglobulin E immunoblot. 3, lupin; 4, vetchling; 5, chickpea; 6, peanut; 7, soy. C, immunoblot inhibition. 8, patient serum; 9, serum preincubated with lupin; 10, serum preincubated with vetchling.

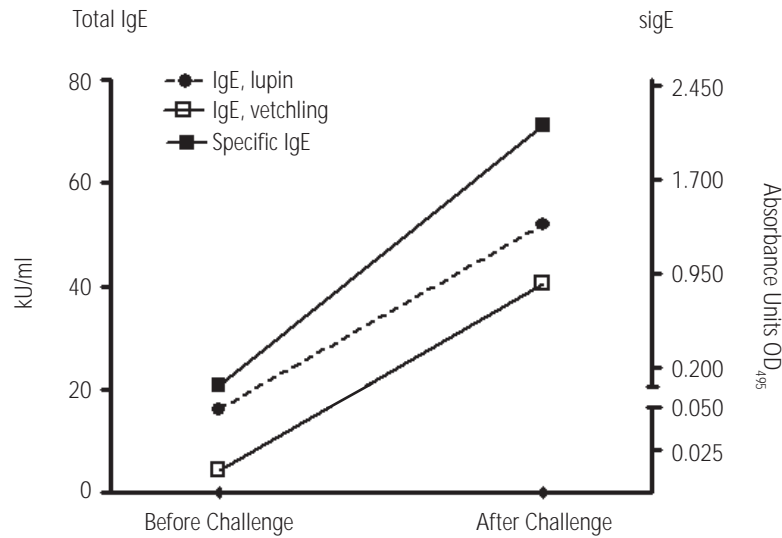


Figure 2. Total lupin-specific and vetchling-specific immunoglobulin (Ig) E before and after inhalation challenge. OD indicates optical density.

extracts of peanut, lentil, chickpea, green bean, white bean, pea, soy, tomato, apple, mustard, wheat, barley and rye flour, almond, hazelnut, walnut, milk, egg, *Anisakis simplex*, and latex were all negative. Prick-to-prick tests were positive for lupin seed (wheal diameter, 7 × 5 mm) and ready-made tomato sauce (brand, Apis) (wheal diameter, 6 × 5 mm) and negative for spices (pepper, oregano, basil, and nutmeg). Finally, skin prick tests with lupin and vetchling flour extracts prepared at our laboratory (1 mg/mL) were both positive (wheal diameters, 12 × 12 mm and 13 × 7 mm respectively).

Total immunoglobulin (Ig) E (CAP system, Pharmacia, Uppsala, Sweden) was 16.2 kU/L and specific IgE was detected for lupin (2.65 kU/L). No specific IgE antibodies were detected for peanut, lentil, chickpea, green bean, white bean, pea, soy, tomato, apple, mustard, wheat, barley and rye flour, almond, hazelnut, walnut, milk, egg, *Anisakis simplex*, *Echinococcus granulosus*, or latex. Enzyme-linked immunoabsorbent assay (ELISA) yielded weakly positive IgE levels for lupin and negative levels for vetchling and flour extracts.

The manufacturers of the commercial ham and cheese sandwich (Jovi) and the ready-made tomato sauce (Apis) the patient had consumed confirmed the presence of lupin flour in these products. The chocolate waffles to which the patient had developed an allergic reaction are no longer commercially available.

An inhalation exposure test with ground lupin seeds, tipped from one tray to another, was performed following measurement of baseline forced expiratory volume in 1 second (FEV<sub>1</sub>), peak expiratory flow (PEF) (both normal) and a methacholine challenge test (negative). After 5 minutes of exposure, the patient developed itching of the nose, ears, eyes, and throat as well as watery rhinorrhea and nasal stuffiness. The test was stopped. FEV<sub>1</sub> and PEF were measured every 30 minutes for the following 2 hours and every 60 minutes for the following 3 hours. The patient was instructed to

measure hourly PEF with a peak flow meter at home. The nasal symptoms disappeared over the afternoon and there was no cough, wheezing, or dyspnea. FEV<sub>1</sub> and PEF showed no significant decreases from baseline, although the methacholine challenge test was positive 24 hours later (20% decrease in FEV<sub>1</sub> from baseline with 3 mg/mL), so the provocation test was considered positive.

Four weeks after the lupin exposure test, total IgE had increased from 16.2 to 52 kU/L and lupin-specific IgE from 2.65 to 29.7 kU/L. ELISA also showed high levels of lupin-specific IgE (2.189 absorbance units [AU], optical density, 495 nm) and was also positive for vetchling flour (0.870 AU) (Figure 1).

Lupin and vetchling flour proteins were resolved using 12.5% sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred to a polyvinylidene fluoride microporous membrane. The immunoblot detected multiple IgE-binding proteins of between 10 and 40 kDa. No allergenic bands were observed with pea, peanut, or soy extracts. The immunoblot inhibition study revealed an intense inhibition of lupin proteins by vetchling flour, proving their allergenic identity (Figure 2).

## Discussion

We have presented a case of recurrent anaphylaxis due to lupin used as a hidden food allergen in a patient with subclinical pollen allergy. The chronology of symptoms and a positive inhalation exposure test to lupin suggest that primary sensitization occurred via the inhalation of ground lupin at the patient's family home.

Considering that the patient experienced severe, recurrent anaphylaxis episodes, the marked increase in total and lupin-specific IgE levels after inhalation exposure and the low

previous levels of total and specific IgE are remarkable. One possible explanation is that antigen presentation to B cells might be more efficient in the respiratory tract mucosa than in the digestive tract mucosa, probably due to the digestive process.

The patient tolerated and tested negative to other legumes such as peanuts, lentils, peas, green and white beans, chickpeas, and soy. Skin and in vitro tests, however, showed cross-reactivity with vetchling, a legume that the patient had never consumed. Immunoblot analysis revealed multiple bands but none of the allergens were shared with legumes other than vetchling.

The first case of lupin allergy was reported by Hefle et al [1] in 1994 in a 5-year-old girl with peanut allergy who developed urticaria and angioedema after eating spaghetti fortified with lupin flour. Since then, many cases of allergy to lupin flour as a hidden allergen in a range of foods such as ready-made tomato sauce (*tomate frito*), biscuits, onion rings, pizza, and chicken bouillon cubes have been reported [2-5]. Although the majority of cases reported were produced by food ingestion, respiratory symptoms following inhalation of lupin dust have also been described [6,7].

Lupin allergy is generally associated with sensitization to other legumes, (mainly peanut) [2,5,7,8]. There have been reports of clinical symptoms due to lupin in between 4% and 28% of patients with peanut allergy, with rates varying according to the gastronomic habits and date of authorization for the use of lupin flour in manufactured foods in each country [9-11]. There have also been reports of allergy to lupin with tolerance to other legumes [4-6,12]. We believe that our case is remarkable in that it is the first report of exclusive (and very strong) cross-reactivity between lupin and vetchling. Vetchling flour consumption is not common in many countries and cross-reactivity with vetchling has not been evaluated.

Multiple IgE-binding proteins with molecular weights of between 10 and 80 kDa have been identified by immunoblotting in both patients with allergy to lupin and other legumes and patients with lupin allergy alone [3-6,8,12-14]. Moneret-Vautrin et al [14] identified a 43-kDa IgE-binding protein, possibly corresponding to conglutin- $\gamma$ , in a patient with known peanut allergy that was completely inhibited by peanut extract. De Las Marinas et al [4], in turn, described a 29-kDa band in a patient with isolated lupin allergy, and Wüthrich et al [5] identified a 50-kDa band that was not inhibited by peanut extract in a patient with lupin allergy who tolerated other legumes. More recently, Goggin et al [15] identified conglutin- $\beta$ , designated as lup an 1, as a major allergen of lupin.

In conclusion, we have presented a case of recurrent anaphylaxis caused by a hidden food allergen preceded by former sensitization via inhalation. Further studies are needed to determine which lupin allergens might predict tolerance to other legumes and which might be related to legume polysensitization.

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