Pompholyx Induced by Intravenous Immunoglobulin Therapy

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Palabras clave: Inmunoglobulina, tratamiento. Pompholyx. Eczema dishidrótico. Reacciones adversas.

Intravenous immunoglobulin (IVIg) therapy is increasingly used to treat a variety of immune mediated disorders [1], including several neurological conditions [2]. It is relatively safe and often effective for patients unresponsive to other therapies. Adverse reactions are usually minor and are said to affect no more than 10% of patients [3]. Various skin reactions (urticaria, leukocytoclastic vasculitis, baboon syndrome, erythema multiforme, petechiae, alopecia, flushing, palmar pruritus, hyperhidrosis, eczematous dermatitis, and dyshidrotic eczema or pompholyx) have been described [4-8].

A 40-year-old woman diagnosed with autoimmune cerebellar disease was treated with a 5-day course of IVIg therapy (Flebogamma 5%, Instituto Grifols SA, Parets del Vallès, Spain) at the standard dose of 0.4 g/kg/d. On the last day of the first cycle of 5 days, an acute reaction involving pruritic erythematous papules and vesicles appeared on her palms. No other drugs were taken before or during treatment. The lesions persisted for more than 2 weeks. Before the next cycle 6 months later, a course of antihistamines (dexchlorpheniramine) was added to the treatment in order to prevent the lesions, but a similar reaction occurred, this time also affecting the right side of the face and with mild general symptoms (malaise and febrile sensation). Topical steroids were prescribed and the lesions subsided again after 2 weeks. The patient was then referred for further evaluation.

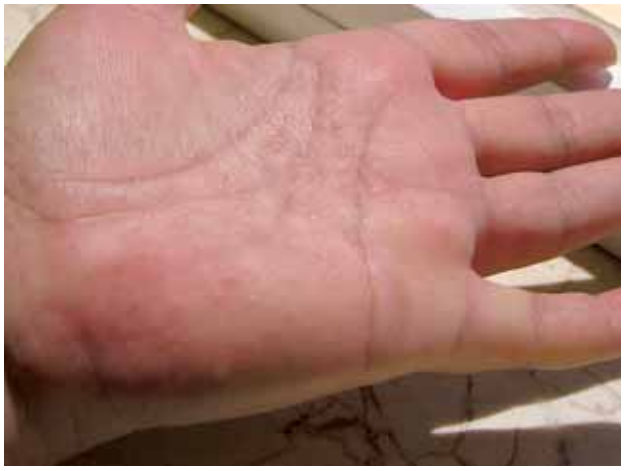
The patient had a history of an eczematous reaction on her hands after the use of perfumed soap several years before the consultation but reported no other skin or allergic conditions. Patch tests with the Spanish standard battery of the Spanish Contact Dermatitis Investigative Group (GEIDC), immunoglobulin (Flebogamma 5%, Instituto Grifols SA, Parets del Vallès, Spain) (on back and palms) and with artificial leather "as is". Prick and intradermal tests were performed with immunoglobulin (1/100, 1/10 in phosphate buffered saline and "as is"). Artificial leather was tested because of a topographic correlation between the lesions (palms and right side of the face) and the areas of skin in contact with the artificial leather of the armchair where the patient had rested during the infusion.

All tests were negative upon immediate and delayed reading (96 hours and 1 week), except for the fragrance mix. This positivity (+) was interpreted as having past relevance, but its present relevance (indirect exposure to another patient's perfume in the leather) could not be ruled out. A third cycle of IVIg therapy without pretreatment and avoiding contact with artificial leather, induced a similar skin reaction that was clearly identified as dyshidrotic eczema of the palms (figure).

IVIg, a relatively safe therapy that provides significant benefits to many patients, has been shown to cause pompholyx or dyshidrotic eczema [6-8], among other adverse skin reactions. Although this reaction is not life threatening, it may cause further distress to patients, who usually complain of invalidating and stressful symptoms, making it important to recognize this reaction as a side effect of IVIg [6].

The pathogenesis of pompholyx is unclear, although antigens ingested or absorbed through direct skin contact may play a role. The high perspiration rate of affected areas of the skin favors a high concentration of potential allergens [9,10]. Further perspiration induced by direct skin contact with artificial leather may favor the development of lesions. Concomitant treatment with antihistamines [8] did not prove useful in this case. As in previously published cases, all skin tests were negative.

Knowledge of the nature of adverse reactions is essential for making clinical decisions and the risk/benefit ratio must be considered. In this case, the continuation of the treatment is under discussion because of doubts about the clinical efficacy but not because of the adverse reaction. Concomitant treatment with topical steroids and avoiding prolonged direct contact with synthetic surfaces have been suggested for the next cycle.



Dyshidrotic eczema.

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Montelukast in 2 Atopic Patients With Intolerance to Nonsteroidal Anti-Inflammatory Drugs and Paracetamol: 5-Year Follow-Up

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Key words: Meloxicam. Montelukast. Nonsteroidal anti-inflammatory drug hypersensitivity. Paracetamol. Tolerance.

Palabras clave: Meloxicam. Montelukast. Hipersensibilidad a antiinflamatorios no esteroides. Paracetamol. Tolerancia.

Hypersensitivity to acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) is a relatively common condition in patients with chronic urticaria and in adults with asthma [1], with a self-reported prevalence of less than 2% in the general population [2]. Increased production of cysteinyl leukotrienes due to the interference of NSAIDs with cyclooxygenase (COX) metabolism is a possible physiopathological pathway underlying the clinical manifestations [3]. In recent years, COX-2 selective inhibitors have been proposed as valid alternatives for patients with hypersensitivity to ASA or NSAIDs [4]. However, in a small percentage of very sensitive patients who may also react to paracetamol, which is a very weak COX inhibitor, even these new drugs are not tolerated and this problem is a challenge in clinical practice [5,6].

The authors report the clinical data from a period of 5 years for 2 asthmatic patients with sensitivity to multiple NSAIDs (including COX-2 selective inhibitors and paracetamol). We present the outcome of administration of montelukast, a leukotriene receptor antagonist, which was also indicated for the control of their mild respiratory atopic disease.

Both patients were females, aged 30 and 41 years. They were referred for a 10-year history of severe generalized urticaria and angioedema occurring less than 1 hour after the intake of 500 mg of ASA or paracetamol. At the time of referral, due to the progressive severity of the reactions, they did not have any suitable medication to control fever or pain. Both patients had also had persistent rhinitis and mild persistent asthma since childhood. Symptoms were under control with low doses of inhaled steroids. They had normal lung function and were both atopic, both sensitized to mite and 1 to grass and *Parietaria judaica*.

Over a period of approximately 1 month, we performed single-blind placebo controlled challenges with the more selective COX-2 inhibitors available in our market at that time (meloxicam, 7.5 mg, and nimesulide, 100 mg) and also with paracetamol (500 mg); responses were positive (generalized urticaria and angioedema) and were controlled with symptomatic treatment. Subsequently they were started on montelukast 10 mg per day as a single treatment, to treat their mild asthma and rhinitis. After 4 and 6 weeks of treatment, respectively, we performed new single-blind placebo controlled challenges with meloxicam (7.5 mg) and paracetamol (1000 mg), obtaining negative results. Both patients continued montelukast as their single asthma-control therapy, rarely needing to use short-acting bronchodilators for relief. They were also able to take the allowed anti-inflammatory and antipyretic drugs on an as-needed basis with full tolerance.

In both these patients with ASA/NSAID and paracetamol sensitivity, the use of montelukast allowed the as-needed intake of these drugs over a period of 5 years. We have tried the same approach in 3 nonatopic patients with intolerance to paracetamol and NSAIDs, but none of them achieved tolerance to these drugs while using montelukast 10 mg daily for 2 weeks before challenges (data available on request).

Consistent with our results, Pérez et al [7] demonstrated that leukotriene antagonists can inhibit skin reactions at least partially in 60% of patients with reactions related to NSAID use. This has also been shown by other authors [8]. Also in line with our data, more recently Serrano et al [9] reported the efficacy of montelukast in preventing adverse reactions

to NSAIDs, COX-2 selective inhibitors, and paracetamol in a 52-year-old patient. Nevertheless, montelukast could not prevent severe allergic reaction to diclofenac in another case [10].

In conclusion, we report the usefulness of montelukast in providing clinically significant tolerance to paracetamol and meloxicam used on an as-needed basis by atopic asthma patients with hypersensitivity to these drugs. Although not observed in placebo-controlled conditions, these findings were confirmed over a follow-up of 5 years. However, based on our experience this approach does not seem to be effective in nonatopic patients, using a 10-mg dose of montelukast. In patients with NSAID hypersensitivity who have a clinical indication to take these drugs on a regular basis, a tolerance induction protocol could be an alternative.

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Anaphylactic Shock Caused by Tick (*Rhipicephalus sanguineous*)

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Key words: Anaphylaxis. Cross-reactivity. Ticks. *Rhipicephalus sanguineous.*

Palabras clave: Anafilaxia. Reactividad cruzada. Garrapatas. *Rhipicephalus sanguineous.*

Ticks frequently cause human disease by transmitting infectious agents (protozoa, rickettsia, bacteria, and viruses) [1]. Toxic local reactions are common, but systemic immunoglobulin (Ig) E-mediated reactions after tick bites are very seldom reported. Allergy to *Argas reflexus* [2], *Ixodes ricinus* [3], *Ixodes holocyclus* [4] and *Ixodes pacificus* [5] is well documented, but there is only 1 case of allergy to *Rhipicephalus* species in the literature [6]. We now report a case of anaphylaxis due to *Rhipicephalus sanguineous*.

A 58-year-old goatherd was referred to our service for evaluation after he experienced heavy sweating, sickness, chest tightness, dyspnea, and loss of consciousness after a tick bite. On arrival at the hospital during that episode, his systolic blood pressure was 80 mm Hg and oxygen saturation was 88%. He was vomiting and had generalized urticaria. Two ticks were found on his skin. He responded to epinephrine, antihistamines and corticosteroids. Afterwards, he reported to us that he had had a similar reaction after a tick bite 5 years ago and that he had a history of severe, recurrent reactions after tick bites. He had no history of previous allergies or family allergies.

Proteins from the whole body of ticks were extracted with phosphate buffered saline by stirring for 1 hour at 4ºC. The soluble fraction was separated by centrifugation at 22 000g for 20 minutes at 4ºC. The tick extract was then dialyzed against distilled water, filtered, and lyophilized. The protein concentration of the extract (24% wt/wt) was determined (Biorad, Hercules, California, USA).

Specific IgE against tick extract was measured by an enzyme allergosorbent test according to the manufacturer's instructions (Hytec-Specific IgE EIA, Hycor Biomedical Inc, Garden Grove, California, USA).

Protein extract of tick was separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). Separated protein bands were electrophoretically transferred to polyvinylene difluoride membranes. The binding of IgE antibody to allergens was analyzed by Western blot using serum from the allergic patient and antihuman immunoglobulin (Ig) E peroxidase conjugate (Dako, Carpinteria, California, USA). Chemiluminescence detection reagents (Western Lightning Chemiluminescence Reagent Plus, Perkin Elmer, Boston, Massachusetts, USA) was added following the manufacturer's instructions.

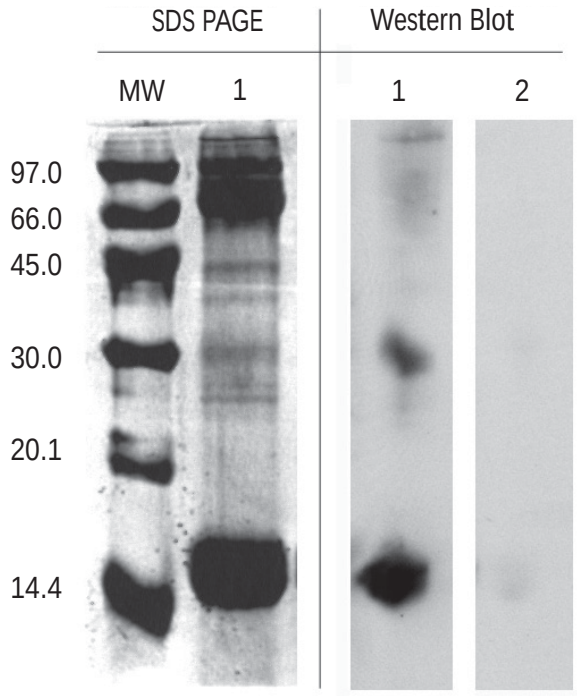
The skin prick test did not indicate sensitization to common inhalants, foods, *Anisakis simplex*, latex, amoxicillin,

insects, or saccaromyces. There was only low sensitization to *Lepidoglyphus destructor*. Laboratory tests revealed only slight leukocytosis (white cell count, 14.3×10^9/L). All other tests (hemostasis, complement system, cortisol, virus serology, and tryptase) were negative. The patient's total serum IgE was high at 716 kU/L by fluorescent-enzyme immunoassay (CAP System IgE FEIA, Phadia, Uppsala, Sweden). The level of specific IgE to destructor was less than 0.35 kU/L. Specific IgE antibodies against *Rhipicephalus* species was 3.4 kU/L .

SDS-PAGE of tick extract showed protein patterns with bands ranging from 14 to 94 kd. The most intense bands were at 15 and 70 kd. The patient's serum IgE antibodies reacted with allergens of 15, 28 and 70 kd, with the 15 and 28 kd allergens revealing the most intense binding (figure).

Adverse reactions to arthropod bites can lead to systemic or local reactions. The most common culprit arthropods are mosquito, flea, horsefly, and tick. Ticks are blood-sucking arthropods of the arachnid class, of which there are 3 families: Nuttaliellidae, Argasidae (soft ticks), and Ixodidae (hard ticks). *R sanguineous*, in the Ixodidae family, is a vector for a wide range of infectious agents affecting dogs. This tick is cosmopolitan in its distribution and, although primarily parasitic on dogs, it accepts a wide range of hosts.

Cross-reactivity among hard tick allergens has been suggested [7]. Acero et al [6] compared the molecular masses of *I holocyclus*, *I pacificus*, and *Rhipicephalus* species, obtaining several common allergenic proteins with molecular masses of 51, 38, 35, and 28 kd [6]. The 107 kd allergen is the most prominent allergen in *I pacificus*, and it appears to be unique to this tick [5]. We obtained an allergenic protein with a molecular mass of 28 kd that is common to other types of ticks, but 2 other proteins of 15 and 70 kd have never been identified before. The 28 kd protein could explain the possibility of cross-reactivity with others types of tick.



Sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and Western blot of tick extract. SDS-PAGE Lane 1: whole-body tick extract; MW indicates the molecular weight standard. Immunoglobulin E immunoblotting of patient serum: Lane 1, 1:1; Lane 2, 1:10.

Cagnoli et al [6] have shown that in sensitized subjects there is a production of IgE to a somatic extract of the tick and to the saliva of the parasite; but a radioallergosorbent test to the latter antigen would be a more sensitive test. In patients sensitized to *Rhipicephalus* species, the value for specific IgE to tick protein obtained in the patient's serum was higher with salivary gland extract than with whole body extract [6]. With another hard tick, *I holocyclus*, higher IgE specific to salivary gland extract than with whole body extract has been reported [9]. These studies suggest that it is more suitable to use salivary gland extract than the whole body extract for diagnostic purposes.

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Severe Anaphylaxis to Royal Jelly Attributed to Cefonicid

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Key words: Allergy. Anaphylaxis. Asthma. Royal jelly.

Palabras clave: Alergia. Anafilaxia. Asma. Jalea real.

Royal jelly, a secretion of the hypopharyngeal and mandibular glands of worker honey bees (*Apis mellifera*), is a creamy yellow–white, acidic material made up of proteins, free amino acids, fatty acids, sugars, vitamins, and some minerals. It is the only food of female bee larvae during early stages of development, but once other larvae have developed into sexually immature worker bees, only the queen bee continues to receive this diet. Although imprecisely defined chemically and generally not standardized, royal jelly is widely used as a health tonic and "alternative" medicine but its beneficial effect in humans is unproven and severe allergic reactions, especially asthma, have occurred following its ingestion [1,2].

We report the case of a 28-year-old man who presented with a 25-year history of asthma that had worsened in recent months to a level of 2 attacks per week and frequent use of salbutamol (up to 15 inhalations per day). The patient experienced dyspnea, wheezing, cough, and chest tightness after intramuscular injection of the fourth dose of Abiocef (cefonicid) prescribed for pharyngotonsillitis. Symptoms disappeared in a few minutes after inhalation of salbutamol. The following day, he had severe dyspnea followed by loss of consciousness within 15 minutes after the fifth dose of Abiocef. He regained consciousness after treatment in the emergency department and it was suggested that he contact an allergy specialist.

Five months later, the patient was referred to our department in order to identify a safe alternative antibiotic drug. He underwent skin prick tests with standard aeroallergens (Stallergénes S.A., Antony Cedex, France) and positive results were obtained with grass pollen, house dust mite, Alternaria, and cat dander. Negative results were obtained in immunoassays to determine the presence of immunoglobulin (Ig) E specific to penicilloyl G and V, ampicilloyl, and amoxicilloyl (UniCAP Pharmacia, Uppsala, Sweden) and in a homemade assay of serum specific IgE to cefonicid using epoxy-activated Sepharose as the solid phase [3]. Total serum IgE concentration was 346 kU/L. However, it emerged during the diagnostic procedure that the patient had ingested royal jelly after each injection of cefonicid. In light of this information, further tests were planned in order to investigate the role of royal jelly in producing the systemic reaction.

A prick-to-prick test with royal jelly gave a positive result with a wheal diameter of 10 mm. The same test was negative in a group of 10 healthy subjects who never ate royal jelly. The presence of serum specific IgE to royal jelly was demonstrated with a homemade radioallergosorbent test using nitrocellulose as the solid phase [4]. Results are considered positive in that assay when specific binding is more than twice the nonspecific binding. Nonspecific binding was evaluated by testing a pool of sera from patients with negative skin tests to royal jelly and was found to be 0.21%. Specific binding was 6.73%, indicating the presence of specific IgE to royal jelly. Negative results were obtained in skin prick tests and intradermal tests with benzylpenicilloyl polylysine and minor determinants mixture (Diater Laboratories, Madrid, Spain), amoxicillin, cefuroxime, and penicillin G, at the concentrations recommended by the European Network for Drug Allergy [5]. Both skin prick tests and intradermal tests with cefonicid were negative. Finally, intramuscular injection of cefonicid was administered to the patient under close clinical supervision and no reactions were observed.

Many people who have experienced an adverse reaction while taking an antibiotic are classified as allergic to the drug without any further investigation. However, overdiagnosis is common due to a fear of anaphylaxis, and as a result, nonallergic patients may be deprived of potentially useful drugs. It is therefore important to diagnose allergic reactions to antibiotics. The findings in the described case show that when an adverse drug reaction is suspected a thorough clinical history and allergy evaluation is needed, and that this should not only include drug allergy tests but also assessment of other allergens such as food. Finally, collaboration between clinic and laboratory is essential.

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Detection of a 12-Kilodalton Lipid Transfer Protein Allergen in Parsley

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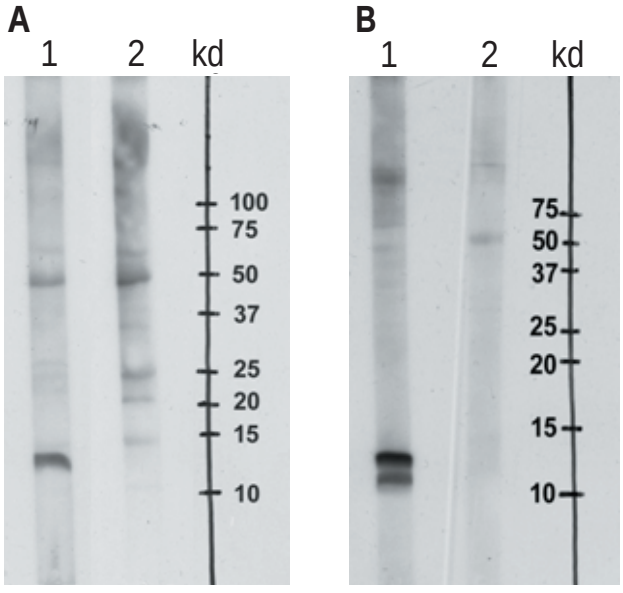
Key words: Allergy. Parsley. Lipid transfer protein.

Palabras clave: Alergia. Perejil. Proteína de transferencia de lípidos.

Parsley (*Petroselinum crispum*) is an herbaceous plant belonging to the Umbelliferae family and is widely distributed worldwide. Despite its frequent consumption, allergic reactions to parsley are uncommon. Previously, urticaria–angioedema [1], anaphylaxis [2], and occupational dermatitis [3] have been described after eating or skin contact with parsley. Recent studies have demonstrated cross-reactivity between some pollen allergens and edible plants [4]. One type of allergen that may be responsible for such cross-reactivity is the family of lipid transfer proteins (LTPs), which are vegetable panallergens mainly found in the outer layers of the plant [5,6].

We report the case of a 26-year-old woman who presented acute rhinoconjunctivitis, facial swelling, otic and oropharyngeal pruritus, and red itchy palms and soles within 5 minutes of eating potatoes with a sauce containing parsley and sweet oil. Treatment with intramuscular corticosteroids and antihistamines led to improvement of symptoms within a few hours. Subsequently she has tolerated potatoes and sweet oil. Furthermore, she reported facial swelling after eating foods such as peanuts, chestnut, grapes, apple, watermelon, melon, and peach.



Western blots of parsley extract: lane 1, with the patient's serum (A) or with a Pru p 3-specific polyclonal antiserum (B); lane 2, negative control without patient's serum or polyclonal antiserum. kd indicates kilodalton.

Skin prick tests (SPT) with a standard panel of aeroallergens (ALK-Abelló SA, Madrid, Spain) were negative, while SPT with peanuts, chestnut, apple, melon, and peach were positive. Prick-to-prick tests elicited a positive response to parsley (4 mm) in the patient, while the results were negative in 5 control subjects. Total serum immunoglobulin (Ig) E concentration was 22 IU/mL. Levels of specific IgE antibodies against parsley assessed by immunoassay (Pharmacia CAP System, Uppsala, Sweden) were 0.435 kU/L, while no specific IgE was found against peanuts, chestnut, apple, grapes, melon, or watermelon.

Fresh parsley was lyophilized and then extracted for 90 minutes at 4°C with sodium chloride. Following centrifugation, the supernatant was filtered and stored at –20°C. Western blotting of protein extract from parsley was performed with the patient's serum and with a polyclonal rabbit antiserum raised against the peach LTP, Pru p 3 (see figure). Negative controls were performed with bovine serum albumin and with preimmune serum from the same rabbit used to obtain the Pru p 3 antibody. Specific IgE levels against Pru p 3 were measured with the quantitative specific IgE assay ADVIA Centaur (Bayer Diagnostics, Tarrytown, New York, USA).

Serum from the patient recognized a previously undescribed low–molecular-weight allergen of 12 kilodaltons (kd). The molecular weight of the allergen suggested that it belonged to the LTP family. We also observed another protein band of 50 kd that appeared both in the presence and absence of the patient's serum. The patient also had specific IgE (2.1 kU/L) to the major peach allergen, Pru p 3, which is an LTP. The presence of an LTP in parsley was confirmed by the recognition of a major band of 12 kd with the Pru p 3-specific polyclonal antiserum.

These data indicate the involvement of an LTP in our patient's parsley allergy. We consider the protein band of 50 kd as nonspecific binding of the secondary antibodies used in the immunoblotting assay rather than specific IgE binding. In our experience, this artefact can be observed when analyzing some extracts, mainly from vegetable foods. In contrast, the 12-kd band was only observed in the presence of the patient's serum. That band therefore represented true IgE binding and could be considered an allergen.

Sensitization to LTPs could be responsible for some of the multiple food reactions suffered by our patient. The potential of LTPs to cause severe allergic reactions to food is well known [7]. However, there are very few reports regarding allergy to parsley and to the best of our knowledge this is the first report of an LTP involved in parsley allergy.

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Anaphylaxis Induced by Lupine as a Hidden Allergen

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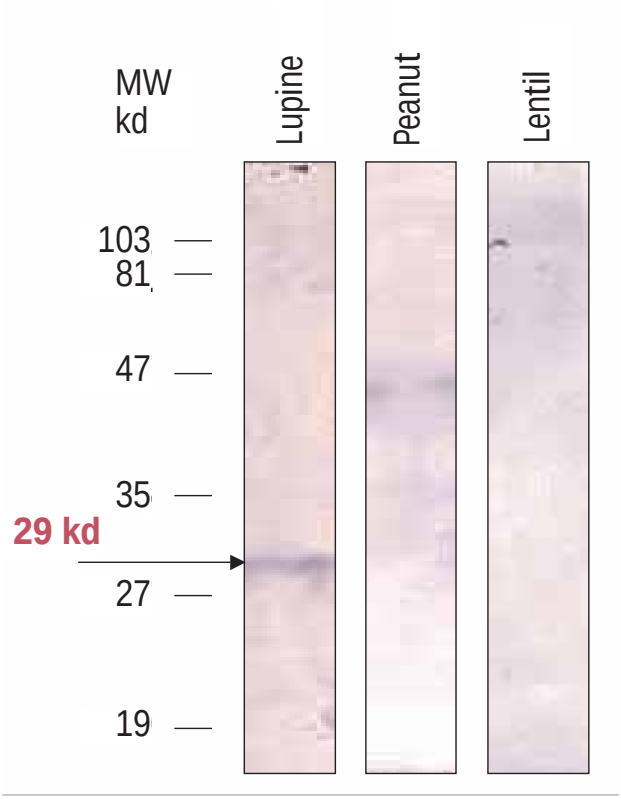
Key words: Lupine allergy. Immunoblotting. Basophil activation test. CAP inhibition. Hidden allergen.

Palabras clave: Alergia a altramuz. Immunoblotting. Test de activación de basófilos. CAP inhibición. Alérgeno oculto.

Lupine (*Lupinus albus*) is a leguminous plant that is usually eaten as an appetizer or made into flour to be added to a variety of baked products. We describe the case of a patient who developed a hypersensitivity reaction immediately after eating a processed food that contained lupine, which had not been mentioned on the label but whose inclusion was later confirmed by the manufacturers.

A 41-year-old woman with no history of allergy presented with a granular feeling at the bottom of her tongue, general malaise, nasal blockage, coughing attacks, palmoplantar pruritus, vomiting, and wheal and flare lesions on limbs. The signs developed after she ate packaged buns of a type she had previously tolerated. Four years earlier, she had experienced dry cough, dyspnea, and dysphagia after the ingestion of lupine beans as an appetizer. The patient tolerated other legumes such as peanuts, lentils and other beans.

Skin tests were performed with a pool of inhalant and food allergens including leguminous plants (soy, peanut, lentil, chickpeas, peas, and lupine), nuts (sunflower seeds and hazelnut), and wheat flour. Positive reactions were observed only to olive pollen (wheal, 5× 7 mm) and lupine (4 × 5 mm). After a prick-to-prick skin test performed with ground buns (made with wheat flour, soy oil, sunflower seeds, salt, natural baking powder, peanut traces, sesame), a papule of 3 × 3 mm was observed. Total serum immunoglobulin (IgE determination (CAP-FEIA, Phadia, Uppsala, Sweden) (56.3 kU/L) and specific IgE to peanut, peas, chickpeas, beans, lentils, soy, sunflower seeds, hazelnut, wheat flour, sesame, and baking powder (<0.35 kU/L), olea (0.16 kU/L), and lupine (2.65 kU/L) were performed. The basophil activation test (BAT) was positive to lupine, beans, chickpeas, and soy (85%, 88.6%, 54.4% and 93.9% activation respectively), and negative to lentils and peanuts (20.3% and 22.9%). Sodium dodecyl sulfate polyacrylamide gel electrophoresis with subsequent immunodetection in the patient's serum was negative to peanut and lentil but detected a 29 kd IgE-binding band, corresponding only to the lupine protein (figure). Cross reactivity with peanuts, previously described in the literature [1] was ruled out by means of (CAP-FEIA) inhibition.



Immunodetection in sodium dodecyl sulfate polyacrylamide gel electrophoresis immunoblotting with anti-immunoglobulin E antibodies in the patient's serum.

In this description of lupine-induced anaphylaxis with tolerance to other leguminous plants, lupine was eaten as a hidden allergen in a commercial product. Subsequently, it was found that the manufacturers of the buns occasionally use lupine flour to enhance their products and do not report its use on their labels. In vitro tests confirmed sensitization to lupine, even though the BAT was positive to other legumes tested, except peanut and lentil. Similar discrepancies between the in vitro study and clinical manifestations in a lupine-allergic patient were also reported by Matheu et al [2]. Follow-up of our patient's course will reveal whether the BAT findings

indicated clinically irrelevant sensitization or predicted future clinical reactivity with other legumes.

The special contribution of this case report is that it shows the presence of a unique 29 kd IgE-binding band to lupine that has not been described in the literature before now [3,4]. The present European Union legislation does not include lupine in the compulsory list of ingredients liable to cause anaphylactic shock (Directive 2003/89/CE of the European Parliament and Council of November 10, 2003 on the labelling of foodstuffs). However, in this regard, a request by the Commission that the scientific panel on dietetic products, nutrition, and allergies evaluate lupin for labeling purposes [5] led to the panel's recommendation to require the inclusion of this allergen.

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Immediate Hypersensitivity to Corticosteroids: Finding an Alternative

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Key words:Corticosteroids. Cross-reactivity. Hypersensitivity. Skin tests.

Palabras clave: Corticoesteroides. Reactividad cruzada. Hipersensibilidad. Pruebas cutáneas.

While corticosteroids are widely used in the management of several diseases as a result of their antiinflammatory and immunomodulatory properties, they can also cause allergic reactions [1], most frequently contact dermatitis due to topical sensitization [2]. Although immediate hypersensitivity to corticosteroids is uncommon, it can lead to life-threatening reactions [3-5]. There are approximately 100 published reports of immediate hypersensitivity reactions occurring after oral and parenteral corticosteroid administration [5,6]. Here, we report 4 patients with immediate reactions to corticosteroids.

After obtaining informed consent from the patients we performed skin tests (skin prick tests and intradermal tests) with hydrocortisone, prednisolone, methylprednisolone, betamethasone, and dexamethasone in all patients. Skin prick tests with corticosteroids were negative in all of the patients, while intradermal tests were always positive with the corticosteroids suspected to have caused the reaction. Negative intradermal tests to other corticosteroids (table) allowed us to select 1 for use in single-blind, placebo-controlled challenge tests, in which increasing doses were administered at 30-minute intervals, in order to identify alternative corticosteroids. Skin tests performed in 10 controls were all negative.

The first case involved a 78-year-old woman with chronic lymphocytic leukemia since the age of 76. She reported 3 episodes of generalized urticaria 30 minutes after oral treatment with chlorambucil and prednisolone, with complete regression 4 hours after oral hydroxyzine. Intradermal tests were positive with prednisolone and methylprednisolone but negative with the other 3 corticosteroids. Challenge tests with oral (5 mg, 10 mg, 15 mg, and 30mg) and intravenous (5 mg, 10 mg, 20 mg, 40 mg, and 75 mg) hydrocortisone were negative. The patient resumed chemotherapy with chlorambucil and hydrocortisone without any adverse events.

Case 2 involved a 28-year-old woman with mild persistent asthma since the age of 12 who received 200 mg of intravenous hydrocortisone succinate for asthma exacerbation. After 15 minutes she developed generalized urticaria. She was treated with hydroxyzine with complete resolution in 2 hours. Intradermal tests were positive with hydrocortisone succinate and negative with the other 4 corticosteroids. Oral challenge with prednisolone (5 mg, 10 mg, 15 mg, and 20 mg) was also negative. Since then, the patient has received oral prednisolone for asthma exacerbations without any adverse events.

Case 3 involved a 30-year-old woman with severe persistent asthma since the age of 4. Twenty minutes after receiving 80 mg intravenous methylprednisolone succinate for asthma exacerbation she developed facial angioedema and generalized urticaria. She was treated with hydroxyzine with complete resolution in 4 hours. Intradermal tests were positive with methylprednisolone succinate and negative with the other 4 corticosteroids. Oral challenge with prednisolone (5 mg, 10 mg, 15 mg, and 20 mg) was negative. Since then, the patient has received oral prednisolone several times for asthma exacerbations, without any adverse events.

Case 4 involved a 39-year-old woman with multiple sclerosis since the age of 29, treated daily with glatiramer acetate, gabapentin, and amantadine and corticosteroid pulse therapy at least twice a year. Ten minutes after receiving 1000 mg of intravenous methylprednisolone succinate she developed generalized pruritus and urticaria, palpebral edema, dysphonia, and hypotension (anaphylaxis). She received

Results of Skin Tests and Challenge Tests in 4 Patients With an Allergic Reaction to Corticosteroids*

	Culprit Drug	Test Results				
		Hydrocortisone succinate SPT (100 mg/mL) ID (1mg/mL)	Prednisolone succinate SPT (10 mg/mL) ID (0.1 mg/mL)	Methylprednisolone succinate SPT (40 mg/mL) ID (0.4 mg/mL)	Betamethasone phosphate SPT (6 mg/mL) ID (0.06 mg/mL)	Dexamethasone phosphate SPT (5 mg/mL) ID (0.05 mg/mL)
Patient 1	Prednisolone	SPT: negative ID: negative CT: negative	SPT: negative ID: positive CT: np	SPT: negative ID: positive CT: np	SPT: negative ID: negative CT: np	SPT: negative ID: negative CT:np
Patient 2	Hydrocortisone	SPT: negative ID: positive CT: np	SPT: negative ID: negative CT: negative	SPT: negative ID: negative CT: np	SPT: negative ID: negative CT: np	SPT: negative ID: negative CT: np
Patient 3	Methylprednisolone	SPT: negative ID: negative CT: np	SPT: negative ID: negative CT: negative	SPT: negative ID: positive CT: np	SPT: negative ID: negative CT: np	SPT: negative ID: negative CT: np
Patient 4	Methylprednisolone	SPT: negative ID: positive CT: np	SPT: negative ID: negative CT: negative	SPT: negative ID: positive CT: np	SPT: negative ID: positive CT: np	SPT: negative ID: negative CT: np

*SPT indicates skin prick test; ID, intradermal test; CT, challenge test; np, not performed.

intramuscular epinephrine and intramuscular hydroxyzine with complete reversal of symptoms in 1 hour. Intradermal tests were positive with methylprednisolone succinate, hydrocortisone, and betamethasone and were negative with prednisolone and dexamethasone. Challenge tests with oral (5 mg, 10 mg, 15 mg, and 20 mg) and intravenous (5 mg, 10 mg, 15 mg, 30 mg, and 40 mg) prednisolone were both negative. Since then, the patient has received prednisolone pulse therapy for multiple sclerosis exacerbations without any adverse events.

In the described cases, both symptoms and skin tests suggested immunoglobulin E-mediated hypersensitivity to corticosteroids. Given that cross-reactions between different corticosteroids have been reported [3], intradermal tests with other corticosteroids should be performed to identify alternative drugs. However, the sensitivity and specificity of these tests remain to be established [6]. In all our patients, it was possible to find an effective and safe alternative corticosteroid, suggested by negative intradermal tests and confirmed by negative challenge tests. We also found some degree of cross-reactivity between the different corticosteroids in intradermal tests. However, the clinical relevance of those cross-reactivities could not be demonstrated because we did not perform systematic challenge tests. Although further studies are needed, our findings clearly indicate the usefulness of intradermal tests for the selection of safe alternative corticosteroids.

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