Fatal Intraoperative Anaphylaxis After Aprotinin Administration

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Key words: Anaphylaxis. Aprotinin. Aprotinin-specific immunoglobulin G and E antibodies. Tryptase.

Palabras clave: Anafilaxia. Aprotinina. Anticuerpos específicos frente a aprotinina inmunoglobulina G e E. Triptasa.

Aprotinin is a 6512-dalton bovine peptide antifibrinolytic agent. Due to its inhibitory effect on proteolytic enzymes (trypsin, plasmin, kallikrein), it is used to reduce blood loss and transfusion requirements and to limit the systemic inflammatory response in major surgery under extracorporeal circulation (cardiac surgery, lung and liver transplantation, hip replacement). The frequency of allergic reactions to aprotinin has been estimated at 2.8% when patients are re-exposed to this peptide within a 6-month period [1, 2].

We present the case of a 76-year-old man with no history of previous allergic diseases who underwent aortic valve replacement due to prosthetic valve endocarditis. Remifentanil, fentanyl, etomidate, midazolam, atracurium, and cefazolin were given during anesthesia. Sixty minutes after induction, intravenous aprotinin (Trasylol, Bayer AG, Levercusen, Germany) was administered; it induced immediate hypotension, pulmonary hypertension, ventricular fibrillation and cardiorespiratory arrest. The patient died after 2 hours of advanced cardiopulmonary resuscitation. When aprotinin had been administered intravenously 2 months earlier, tolerance had been good.

Serum tryptase levels measured 167 μg/L and 3.8 μg/L (CAP Pharmacia, Uppsala, Sweden) at the time of the adverse reaction and 1 day before surgery, respectively. A peroxidase-based enzyme-linked immunosorbent assay demonstrated the presence of specific immunoglobulin (Ig) E to aprotinin in serum. The absorbance measured at 495 nm was 0.728 optical density (OD) in contrast with 0.090 OD for the mean of the control sera from 3 patients.

This is a case of fatal anaphylaxis due to aprotinin demonstrated by the presence of serum specific IgE. Serum tryptase measurement was essential for the diagnosis of anaphylaxis.

It has been recommended to avoid re-exposure to aprotinin for at least 6 months, since it has been proven to be a main risk factor for anaphylactic reactions [1-3]. Re-exposure to aprotinin within a 2-month period may have been a determinant for this fatal reaction.

Standardized enzyme immunoassay kits are commercially available for the quantitative determination of antiaprotinin IgG antibodies (CellTrend, Luckenwalde, Germany). We propose that the determination of specific IgE, and especially IgG, to aprotinin should be evaluated in patients with prior contact with this peptide. Patients with high antibody titers should be considered at risk, whereas the absence of aprotinin-specific IgG has been reported to indicate low risk of a hypersensitivity reaction [1-3]. Recently, the Spanish Drug Agency has issued an official bulletin recommending that IgG specific antibodies be determined prior to aprotinin administration. They also stress that aprotinin administration is contraindicated in patients in whom specific-IgG antibodies are detected as well as in patients possibly exposed to aprotinin within the last 12 months.

Recent publications indicate that the use of aprotinin is associated with a dose-dependent higher risk of renal failure and multiorgan damage, including heart and brain injury. The risk of long-term mortality is also higher after the use of aprotinin in comparison with the use of lysine analogs aminocaproic acid and tranexamic acid. It has therefore been suggested to use those safer and cheaper alternatives and to withdraw aprotinin from human use [4-6].

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Use of the Comet Test to Assess DNA Damage in Children With Ataxia-Telangiectasia and Their Relatives

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Key words: Ataxia-telangiectasia. DNA damage. Cancer risk. Comet test.

Palabras clave: Ataxia-telangiectasia. Daño en el ADN. Riesgo de cáncer. Prueba cometa.

Ataxia-telangiectasia is a hereditary autosomal recessive disease characterized by immune deficiency and an increased incidence of tumors. The mutated gene responsible for the disease has been identified. It is known as ataxia-telangiectasia mutated (*ATM*) and is located on the long arm of chromosome 11 (11q22-23). This gene controls the production of an enzyme involved in cell responses and the control and repair of the cell cycle [1]. In healthy carriers of *ATM*, an increased risk of cancer has been noted that seems to be related to greater chromosomal instability, and it has been suggested that the identification of these heterozygotes would make it possible to include them in cancer screening programs and would permit use of more appropriate cytostatic treatments of cancer [2].

Chromosomal instability and cell damage can be estimated using various techniques [3,4]. In this study, we used the comet test to assess DNA damage in lymphocytes from children with ataxia-telangiectasia, and to measure chromosomal instability within the family. Seventeen subjects were studied: 4 patients diagnosed with ataxia-telangiectasia, 3 family members, and 10 healthy children. Blood samples were obtained by venous puncture and lymphocytes were obtained by standard methods. The cells were embedded in agarose on microscope slides and placed in an electrophoresis tank with an alkaline buffer to allow separation of the DNA chains. Once electrophoresis was complete, the slides were stained with 4',6-diamidino-2-phenylindole (DAPI). The DAPI-stained nuclei in each gel were examined by UV microscopy using Komet 5.1 imaging software (Kinetic Imaging Ltd, Liverpool, UK). The following data were obtained: visual appearance of DNA (Figure), olive tail moment (product of tail length and fluorescence intensity), and the percentage of DNA in the tail. Statistics were performed with SPSS version 13.0. The Kruskall-Wallis test was used to compare variables between groups.

The mean (SD) number of DNA fragments assessed visually was higher in patients (131.5 [0.2]) than in controls (15 [9.6]), and the difference was statistically significant ($P < .05$). The same was true for the olive tail moment values (0.31 [0.5] vs 0.16 [0.2]) and the percentage of DNA in the tail (17% [6%] vs 10% [5%]). The highest values for chromosome instability were obtained from a patient with ataxia-telangiectasia who had developed acute lymphoblastic leukemia. That patient had a visual score of 233, an olive tail moment of 0.44, and 23% DNA in the tail.

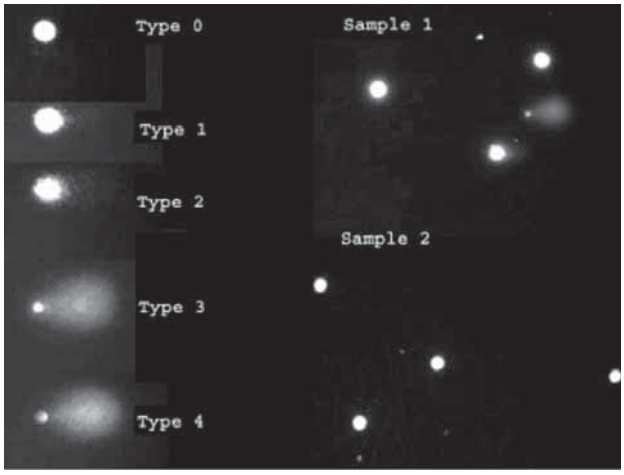

Figure. Fluorescent microscope images of the different types of cell damage. Damage ranges from type 0 (no damage) to type 4 (maximum damage). Sample 1, nuclei of lymphocytes from a patient with DNA damage; sample 2, nuclei from a healthy control individual.

The 3 family members studied also had increased values for DNA fragmentation. These values were higher than the mean found in the healthy controls, but lower than those in patients with ataxia-telangiectasia ($P < .05$). DNA fragmentation was higher in the group of family members than in the control group, in terms of the visual score (36 [10.2]), olive tail moment (0.26 [0.3]), and percentage of DNA in the tail (15.5% [3%]).

Genetic diagnosis in ataxia-telangiectasia is performed by sequencing of the ATM gene [5]. It has been reported that healthy carriers of the ATM gene have an increased risk of chromosomal instability and higher incidence of tumors [2]. We used the comet test to show that patients with ataxia-telangiectasia have a higher rate of DNA damage than healthy controls. This chromosomal instability is related to the clinical manifestations in these patients. Our study demonstrates that relatives of patients with ataxia-telangiectasia have higher levels of DNA damage than healthy controls, a finding that is consistent with the higher incidence of tumors in such individuals [6]. Identification of these healthy heterozygotes with the comet test would make it possible to detect patients at high risk of cancer and would permit modification of the cytostatic treatments [7].

We conclude that electrophoresis of cells in alkaline medium (comet assay) is a valid technique for quantifying DNA damage in patients with ataxia-telangiectasia and their relatives.

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Anaphylaxis Due to Metronidazole With Positive Skin Prick Test

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Key words: Anaphylaxis. Metronidazole. Prick test. Cross-reactivity. Imidazole derivatives.

Palabras clave: Anafilaxia. Metronidazol. Prueba cutanea. Reactividad cruzada. Derivados imidazólicos.

Metronidazole is a drug belonging to the 5-nitroimidazole group. It shares a high structural similarity with its derivatives (tinidazole, secnidazole, and ornidazole). It is used to treat trichomonas vaginalis, amebiasis, and anaerobic infections in combination with other antibiotics. The drug is usually well involve tolerated; the most common side effects involve gastrointestinal symptoms, reversible hematological alterations, and disorders of the central nervous system. Hypersensitivity reactions to metronidazole are rarely described. We report a case of anaphylaxis to metronidazole.

A 51-year old woman with no history of allergy was referred to our service for evaluation of a drug reaction. She had been treated with spiramycin and metronidazole (Rhodogil, Sanofi-Aventis, Paris, France) for gingivostomatitis 6 months earlier. Thirty minutes after the first dose in the reported episode, she presented sneezing, rhinorrhea, perioral paresthesia, and upper airway angioedema followed by generalized pruritic erythematous lesions. The symptoms disappeared within a few hours of administration of corticosteroids and antihistamines. She remembered a previous episode of labial angioedema and sneezing 2 hours after the first dose of Rhodogil. She had previously tolerated the drug.

Skin prick tests were performed with erythromycin (250 mg/mL), spiramycin (250 mg/mL) and metronidazole (125 mg/mL) with a positive result for metronidazole on 2 different occasions. Skin prick tests with metronidazole were negative in 10 controls. An oral provocation test with spiramycin (500 mg) was negative. We also performed skin prick tests with other imidazole derivatives such us ketoconazole (20 mg/mL), fluconazole (200 mg/mL), etomidate (2 mg/mL), mebendazole (100 mg/mL), cimetidine (200 mg/mL), famotidine (20 mg/mL), ranitidine (150 mg/mL), ornidazole (500 mg/mL), tiabendazole (500 mg/mL) with negative results. The patient refused oral provocation with metronidazole or derivatives. The positive skin prick test and clinical history strongly suggested anaphylaxis due to metronidazole. To the best of our knowledge, there are no previous reports of metronidazole anaphylaxis.

Reports of hypersensitivity reactions to metronidazole that we have located have mentioned fixed exanthems [1,2]; irritation, pruritus and burning with topical metronidazole [3]; exanthems varying from pityriasis rosea and acute pustulosis to toxic epidermal necrolysis [4,5]; cutaneous exanthems (2 immediate and 2 delayed) [6]; and rhinoconjunctivitis (1 case) and asthma crisis (1 case) [7].

In general, the sensitivity of skin tests is low. Thus, epicutaneous tests have been positive at different concentrations on residual lesions in some cases of fixed exanthems [1,2,7], and skin prick tests with metronidazole have usually been negative [6-8]. We have only found 1 report of a patient with a positive skin prick test that suffered from angioedema and micropapular exanthems on the face, neck and thighs after 4 doses of Rhodogil [6]. Cross-reactions have been reported between metronidazole and tinidazole [9] and between albendazole and metronidazole by oral challenge testing [10]. Others have found a lack of reactivity between metronidazole, tinidazole, tioconazole, albendazole, ketoconazole, and mebendazole by patch testing [8,11]. Generally, only the drug involved in the reaction has been evaluated in clinical studies; Therefore, studies with compounds from all the imidazole series would be useful in order to evaluate their cross-reactivity. Our patient refused oral challenge and, due to the severity of the reaction and because other therapeutic alternatives are available, we recommended avoiding all the imidazoles.

In conclusion, this case of anaphylaxis to metronidazole was supported by a positive skin prick test suggesting an immunoglobulin-E–mediated mechanism.

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Anaphylaxis to Salbutamol

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Key words: Anaphylaxis. Basophil activation test. Short-acting ß$_2$-agonist. Salbutamol.

Palabras clave: Anafilaxis. Beta-2-agonistas de acción corta. Prueba de activación de basófilos. Salbutamol

Short-acting ß$_2$-agonists are the first-line drugs for treating reversible airway obstruction, such as in asthma and in certain patients with chronic obstructive pulmonary disease. Adverse effects or bronchoconstriction after their use have been documented [1], but to our knowledge no cases of anaphylactic reactions have been reported.

A 42-year-old woman diagnosed with asthma due to pollen was treated with nebulized salbutamol and budesonide after an acute exacerbation. Ten minutes later, she experienced generalized itching and erythema, eyelid swelling, chest tightness, nausea, and abdominal pain. She had previously tolerated both drugs.

Skin prick tests and intradermal tests with salbutamol and budesonide were negative. The patient signed an informed consent statement for drug challenge and was then administered 200 μg and 400 μg of inhaled budesonide at an interval of 1 hour. Tolerance was good. She was later administered 100 μg and 200 μg of inhaled salbutamol. After the second dose, she experienced 10 minutes of facial itching that resolved spontaneously. Afterwards, we decided to challenge with nebulized salbutamol together with budesonide. Five minutes after the administration, she began feeling generalized itching and erythema, eyelid swelling, chest tightness and abdominal pain. A skin prick test to latex was negative and the specific serum immunoglobulin E (IgE) titer was less than 0.35 kU/L. The patient was then separately challenged with inhaled placebo, nebulized saline solution, and nebulized budesonide, with good tolerance. After the challenge with nebulized salbutamol, she again experienced generalized itching and erythema, eyelid and palmar swelling, chest tightness, nausea and abdominal pain (Figure). A basophil activation test (BAT) to salbutamol was performed next, but no activation was detected with concentrations of 0.39 μg/mL, 1.56 μg/mL, 6.25 μg/mL or 25 μg/mL. An anti-IgE activation carried out prior the BAT to salbutamol was negative as well. Patch tests

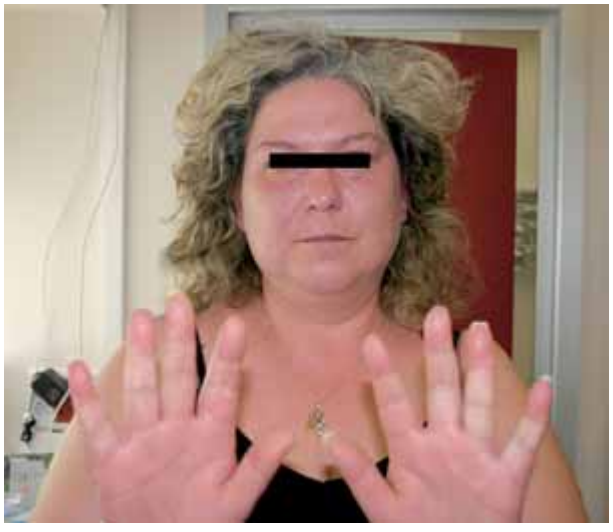

Figure. Generalized erythema and eyelid and palmar swelling after challenge with nebulized salbutamol.

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with salbutamol and terbutaline were also negative. We decided not to challenge with any other short-acting ß$_2$-agonists. Tolerance was good to further challenges with long-acting ß$_2$- agonists (formoterol and salmeterol).

Salbutamol is an adrenergic agonist bronchodilator with a higher affinity for ß$_2$-receptors. In the airway, activation of ß$_2$-receptors results in relaxation of bronchial smooth muscle and a widening of the airway. Its onset of action is rapid, providing relief within 5 to 15 minutes of administration.

Short-acting ß$_2$-agonists are widely used and side effects like tremor, palpitations and headache are commonly described [1]. So-called paradoxical bronchoconstriction to salbutamol has also been documented [2-4]. In a recently reported case of severe bronchoconstriction with different short acting ß$_2$-agonists, an IgE-mediated mechanism was suspected and tolerance to long-acting ß$_2$-agonists was good [5].

In the case we report, the immunological mechanism involved in the reaction remains unclear. BAT is based on the detection of allergen-induced CD63 expression on basophils (a marker of activation) and has proven to be useful in the diagnosis of IgE-mediated allergies. After activation, CD63 can be measured by flow cytometry, using stimulation control with anti-IgE as a positive control [6-8]. However, in the present report, we were unable to demonstrate the immunological pathway since stimulation with anti-IgE showed no activation. Furthermore, even though the short time between the inhalation and the reaction onset and the fact that patient was reproducibly rechallenged, suggesting a type I reaction, IgE antibodies could not be detected.

We present a case of an anaphylactic reaction after salbutamol administration. Physicians must be aware of the possibility that drugs used in the treatment of allergic reactions may occasionally act as the causal agent itself.

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Allergy to Proton Pump Inhibitors: Diagnosis and Assessment of Cross-Reactivity

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Key words: Proton pump inhibitors. Omeprazole. Drug allergy. Hypersensitivity. Cross-reactivity.

Palabras clave: Inhibidores de la bomba de protones. Omeprazol. Alergia a medicamentos. Hipersensibilidad. Reactividad cruzada.

Proton pump inhibitors (PPIs) are modified benzimidazoles that include omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole. They constitute the treatment of choice in acid reflux and peptic ulcer diseases. A few cases of immunoglobulin (Ig) E-mediated hypersensitivity to omeprazole have been reported in which cross-reactivity among all PPIs is frequently assumed [1-3]. We describe a case of anaphylaxis to omeprazole and analysis of cross-reactivity through an exhaustive diagnostic procedure.

A 45-year-old woman presented with acute itching of the palms and soles, diffuse erythema, and breathlessness 3 days after heminephrectomy. An unclear temporal relationship was observed with the intravenous drugs administered: dexketoprofen, ciprofloxacin, ranitidine, metamizole, and omeprazole. Twenty days later, she presented a similar episode with vomiting and diarrhea an hour after ingesting a 20 mg omeprazole tablet for epigastralgia. She was diagnosed with gastroenteritis in the emergency department.

Intradermal and skin prick tests (SPT) were performed with dexketoprofen, ciprofloxacin, ranitidine, magnesium metamizole, and omeprazole. Negative results were obtained with all of the tested drugs except omeprazole. Histamine and saline were used as positive and negative controls, respectively. Controlled oral challenges were performed with dexketoprofen, ciprofloxacin, ranitidine, and metamizole, all

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of which were well tolerated. The patient provided informed consent to the skin tests and oral challenges.

In order to identify alternative treatments, PPIs were tested by SPT and intradermal test. All PPI solutions were prepared in our laboratory under sterile conditions in a horizontal laminar flow cabinet. Solutions were filtered through membranes with a pore size of 0.22 μm. Omeprazole and pantoprazole were prepared at concentrations of 40 mg/mL by dissolving the corresponding lyophilized drugs (Losec 40 mg and Pantocarm 40 mg) in 1 mL of 0.9% saline. Lansoprazole, rabeprazole, and esomeprazole solutions were prepared from enteric-coated tablets (Opiren 30 mg, Pariet 20 mg, and Nexium Mups 20 mg, respectively) by crushing in a mortar and adding 1 mL of 0.9% saline to produce 30 mg/mL, 20 mg/mL, and 20 mg/mL solutions, respectively. The stock solutions were kept at 4°C for no more than 24 hours. SPT was performed directly with the stock solutions and intradermal tests were done with the stock solutions and 3 serial dilutions (1:10, 1:100, and 1:1000, v/v), in each case starting with the lowest concentration and stopping when a positive result was obtained.

SPT was positive for omeprazole (wheal diameter, 16 mm), pantoprazole (6 mm), and rabeprazole (5 mm). Intradermal tests at the lowest dilution (1:1000, v/v) showed a positive result in all cases: omeprazole (15 mm), pantoprazole (11 mm), lansoprazole (10 mm), rabeprazole (8 mm), and esomeprazole (10 mm). Because of the severity of the reaction and the results of the skin tests, we decided not to perform controlled oral challenge tests. SPT and intradermal tests (1:100 and 1:1000, v/v) with the 5 PPIs were performed in 5 nonatopic subjects, with negative results in all cases.

Various doses of PPIs have been used previously in skin tests [3-5]. In our experience, PPI extracts at the concentration described above for SPT and dilutions of 1:100 and 1:1000 for intradermal tests are safe and informative. Other authors have also used similar concentrations for cutaneous tests, showing a high specificity [6].

Although cross-reactivity among PPIs has usually been assumed [1-3], selective allergies to lansoprazole and rabeprazole have recently been reported [5,6]. This selective pattern could be based on the homology between their side chains and not on the common pyridine central ring (Figure). Therefore, 2 different patterns of response seem to exist in PPI allergy, one dependent on the shared pyridine ring that would explain the cross-reactivity among the whole group and the other dependent on the side chain that would explain the selective hypersensitivity to lansoprazole and rabeprazole.

In conclusion, when PPI allergy is suspected, we suggest a study including all PPIs to consider selective oral challenges or avoidance of the whole group, as in our case.

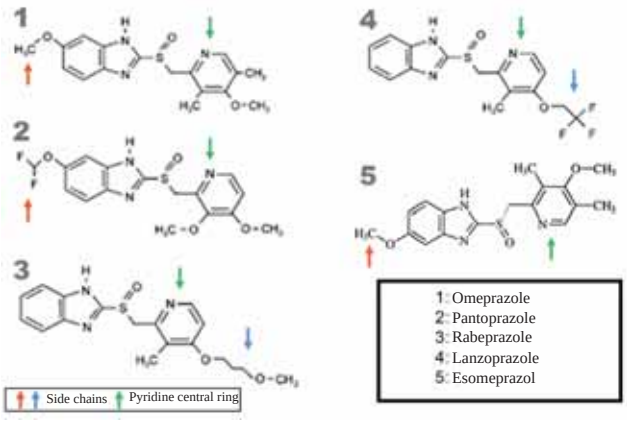

Figure. Chemical structure of proton pump inhibitors.

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Occupational Asthma and Rhinoconjunctivitis Caused by Cricket Allergy

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Allergic occupational asthma can be caused by a number of substances, mostly proteins, derived from animals, plants,

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foods, and enzymes. Insect exposure is not very common in Western countries. However, laboratory workers or other professional groups may have direct contact with these animals. Nowadays, many insect species belonging to different orders have been implicated in allergic processes [1]. It has been estimated that 50% of animal-sensitized individuals will develop rhinoconjunctivitis, 25% skin reactions, and 25% asthma, and most allergic processes in these individuals affect multiple target organs [2,3].

We present a patient with occupational asthma and rhinoconjunctivitis caused by inhaling cricket (*Acheta campestris*) particles and contact urticaria after handling of crickets. A 28-year-old man with no previous personal history of asthma or other respiratory disorders and who had never smoked came to our allergy unit with a 4-year history of frequent episodes of cough, dyspnea, and wheezing accompanied by rhinoconjunctivitis and occasionally chemosis and urticaria. He had worked for 7 years as an assistant in a reptile shop, where he fed reptiles with live crickets, which themselves were fed with cornmeal. He developed the symptoms after a latent period of 3 years. The patient reported improvement of the respiratory symptoms and disappearance of cutaneous symptoms at the weekend and during holidays.

Skin prick tests with a battery of common inhalant allergens, including dust mites, pollens, moulds, cat and dog dander, and insect (German cockroach, oriental cockroach, and American cockroach), were negative. Skin prick test with a manufactured cricket extract at a concentration of 1 mg of freeze-dried material per milliliter was positive (7 mm wheal diameter) and negative in 5 control individuals. Skin prick test (prick by prick) with a cornmeal extract was negative. Spirometric values were in the normal range (forced vital capacity [FVC], 5.18 L [89% of predicted]; forced expiratory volume in 1 second, 4.11 L [89% of predicted]; forced expiratory flow at 25%-75% of FVC, 3.68 L/s [80% of predicted]) and the results of a bronchodilator test were negative. Serial determinations of peak expiratory flow were seen to drop by more than 20% during work periods and returned to normal values at the weekend. A specific nasal challenge test, measured with acoustic rhinometry, was performed with a cricket extract and showed an immediate response at 1:1000 dilution of the extract used in the prick test, with a reduction in nasal volume of more than 30% between the 2nd and 5th centimeter into the nostrils measured at 10 minutes. A nasal challenge with phosphate buffered saline was negative. Specific nasal challenge test with cricket extract was performed in a control patient with a negative result. The protein profile of the cricket extract showed several bands with a molecular weight range of 10 to 100 kDa. Immunoblot experiments showed several bands with immunoglobulin (Ig) E binding capacity. The most prominent bands corresponded to proteins with a molecular weight of 17, 32, 47, and 62 kDa. No bands were recognized with a pool of sera from healthy control individuals (Figure).

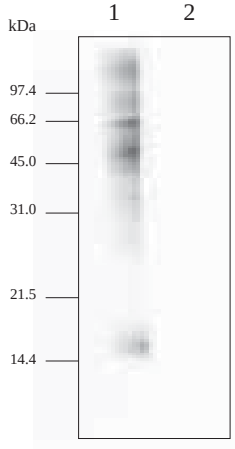

Figure. Immunoblot experiments. Lane 1, patient's serum; lane 2, control serum.

Patients with IgE sensitization to crickets, without evidence of clinical relevance, have been reported in previous studies and most of them showed cross reactivity with other insects [4,5]. Bagenstose et al [6] reported 2 patients whose clinical history strongly suggested an asthma-related allergy linked to their occupation, but the diagnosis was not confirmed by respiratory function tests. Crickets appeared to be involved. The suspected cricket allergy was confirmed by a skin test and bronchial inhalation challenge. However, both patients were sensitized to several common aeroallergens and also other allergens they were exposed to in their jobs, including crickets.

In conclusion, this is the first reported case of unequivocal occupational asthma and rhinoconjunctivitis with contact urticaria in a patient monosensitized to cricket. The clinical relevance was demonstrated by specific nasal challenge test measured by acoustic rhinometry. More studies are necessary to determine the immunochemical characteristics of the allergens and cross-reactivity with other insect groups.

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