Immediate Allergic Reaction Due to Neomycin

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Key words: Allergic urticaria. Aminoglycosides. Neomycin sulphate.

Palabras clave: Urticaria alérgica. Aminoglucósidos. Sulfato de neomicina.

Neomycin is an aminoglycoside that is used as a topical antibiotic, a preservative, and an oral drug. The main adverse effect associated with its use is contact dermatitis, and to date, there have been no reports of immediate allergic reactions. We report the case of a patient, referred to our outpatient clinic, who experienced immediate urticaria following the topical application of neomycin in the nose.

The patient was a 52-year-old man who had experienced recurrent nasal scabs for 10 years. He had repeatedly treated the symptoms himself with Rinobanedif (Química Farmacéutica Bayer S.L., Barcelona, Spain), a nasal ointment with the following ingredients: bacitracin zinc, 50 000 IU; neomycin sulphate,

Table . Sources of Neomycin in Spain

Topical and Oral Preparations		
Antihemorroidal hubber	Leuco hubber	Panotile
Bacisporín	Linitul antibiótico	Poly-pred
Bexicortil	Liquipom dexa-antibiótico	Pomada antibiótica liade
Bio-hubber/fuerte	Maxitrol	Positon crema
Blastoestimulina óvulos	Neo-analsona	Positon crema
Blastoestimulina pomada	Neo-bacitrin	Potison loción
Creanolona	Neo-bacitrin hidrocortisona	Positon ungüento
Decadran neomicina	Neo-hubber	Rinobanedif
Deltacina	Oftalmolosa cusi	Sulfitestin neomicina
Dermisone tri-antibiótica	prednis.neomi.	Synalar ótico
Dermo hubber	Oftalmowell	Tulgrasum antibiótico
Fludronef	Otosporín	Tulgrasum cicatrizante
Fml-neo		Vinciseptil ótico
Vaccines Containing Neomycin		
Inactivated polio: Antipolio oral Wellcome, Oral antipolio llor-evans, Polio Sabin oral	Rubella virus: Antirrubeola Merieux, Llor-evans, Llorente, Antirrubeola MSD, Antirrubeola SKF, Antirrubeola SB, Rubeaten Berna	Rabies vaccine adsorbed: Antirrábica Merieux
Measles, mumps and rubella virus: Rubeaten, Triple MSD, Priorix	Mumps virus: Antiparotiditis MSD	Influenza virus: Mutagrip, Imuvac, Evagrip, Gripavac, Chiroflu, Chiromas, Inflexal, V, Vitagripe, Prodigrip, Vacuna Antigripal Fraccionada
Measles virus: Moraten Berna, Rouvax, Antisarampión Llor-evans, Rimevax Amunovax	Chickenpox: Varicela SFK, Varilrix	
Other Potential Sources of Exposure		
Deodorants, soaps, and cosmetics Dental root canal work Pet foods Veterinary products		

0.50 g (equivalent to neomycin, 0.35 g); prednisolone, 0.30 g; phenylephrine hydrochloride, 0.5 g; chlorbutol, 0.80 g; eucalyptol, 0.20 g; niaouli essence, 0.20 g; petroleum jelly; cholesterin; and paraffin. On the last 2 occasions the patient had used the ointment (at 2-week intervals in the month prior to the visit), he had developed acute facial swelling, pruritus of the eyes, nose, ears, and throat, watery rhinorrhea, nasal congestion, sneezing, and generalized urticaria within 3 minutes of application. The symptoms resolved within a few hours of treatment with intramuscular corticosteroids and antihistamines.

Skin prick tests (SPTs) with a standard panel of aeroallergens were negative. An SPT with Rinobanedif, however, produced a positive wheal of 12 mm (histamine control wheal, 6 mm). No delayed skin reactions were observed. The ingredients of Rinobanedif were obtained from the manufacturer and tested separately by SPT (bacitracin zinc, 10 mg/mL; neomycin sulphate, 10 mg/mL; prednisolone, 10 mg/mL; phenylephrine hydrochloride, 0.25 g; chlorbutol, 10 mg/mL; and eucalyptol, niaouli essence, cholesterin, and undiluted paraffin). All the compounds tested negative except for neomycin sulphate, which produced an 18-mm wheal. SPTs performed with other aminoglycoside antibiotics (tobramycin and gentamicin) were negative, as were SPTs performed in 3 control subjects. The patient refused to undergo a drug challenge study.

Neomycin is an antibacterial agent commonly used for the topical treatment of external ear, skin, and nasal infections. It is often used in association with corticosteroids and other antibacterial agents. Administered orally, the drug can prevent gastrointestinal infections in digestive surgery. Neomycin is also employed as a preservative in vaccines and many other products (Table).

Topical neomycin is a common sensitizer and has been reported to be responsible for 11.6% of all contact dermatitis reactions [1]; this figure has been increasing progressively in recent years and topical neomycin is now among the 10 most common causes of contact dermatitis [1,2] and the most common cause of drug-induced contact dermatitis [3]. The risk of neomycin sensitization is directly related to the frequency of its use and is obviously greater in chronic treatments [4].

Neomycin can cause both delayed eczematous contact dermatitis and generalized reactions such as exfoliative dermatitis and erythroderma; cross-reactions with other aminoglycoside antibiotics can also cause these reactions in neomycin-allergic patients [5]. Our report confirms the involvement of neomycin in immediate rhinoconjunctivitis and urticaria. To the best of our knowledge, this is the first time an immediate reaction induced by neomycin allergy with SPT positivity has been reported.

There have been reports of cross-sensitivity between neomycin and aminoglycoside antibiotics such as framycetin, bacitracin, and polymyxin but cross-sensitivity with gentamicin is rare [4,6]. In our patient, SPT did not reveal sensitization to the other chemically related aminoglycosides tested (gentamicin and tobramycin).

References

1. Pratt MD, Belsito DV, DeLeo VA, Fowler JF Jr, Fransway AF, Maibach HI, Marks JG, Mathias CG, Rietschel RL, Sasseville D, Sherertz EF, Storrs FJ, Taylor JS, Zug K. North American Contact Dermatitis Group patch-test results, 2001-2002 study period. Dermatitis. 2004 Dec;15(4):176-83
2. Wetter DA, Davis MD, Yiannias JA, Cheng JF, Connolly SM, el-Azhary RA, Farmer SA, Fett DD, Johnson JS, Linehan DL, Richardson DM, Schroeter AL. Patch test results from the Mayo Clinic Contact Dermatitis Group, 1998-2000. J Am Acad Dermatol. 2005 Sep;53(3):416-21
3. de Pádua CA, Uter W, Schnuch A. Contact allergy to topical drugs: prevalence in a clinical setting and estimation of frequency at the population level. Pharmacoepidemiol Drug Saf.. 2007 Apr;16 (4):377-84.
4. Menezes de Pádua CA, Schnuch A, Lessmann H, Geier J, Pfahlberg A, Uter W. Contact allergy to neomycin sulfate: results of a multifactorial analysis. Pharmacoepidemiol Drug Saf.. 2005 Oct;14 (10):725-33
5. Le Coz CJ. Hypersensitivity to neomycin. Ann Dermatol Venereol. 2001 Dec;128(12):1359-60.
6. Kimura M, Kawada A. Contact sensitivity induced by neomycin with cross-sensitivity to other aminoglycoside antibiotics. Contact Dermatitis. 1998 Sep;39(3):148-50.

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Allopurinol-Induced DRESS Syndrome in a 13-Year-Old Girl

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Key words: Allopurinol. Drug-induced hypersensitivity syndrome. Drug reaction. Eosinophilia. Liver enzymes.

Palabras clave: Alopurinol. Síndrome de hipersensibilidad inducida por medicamentos. Reacción medicamentosa. Eosinofilia. Encimas hepáticos.

Drug-induced hypersensitivity syndrome is a rare but severe disease with the risk of life-threatening systemic involvement [1]. Multisystem involvement with blood eosinophilia has led to this syndrome being named "drug reaction with eosinophilia and systemic symptoms" (DRESS) [2]. It has been estimated to occur in about 1 in 10 000 exposures to drugs such as antiepileptics, allopurinol, minocycline, and

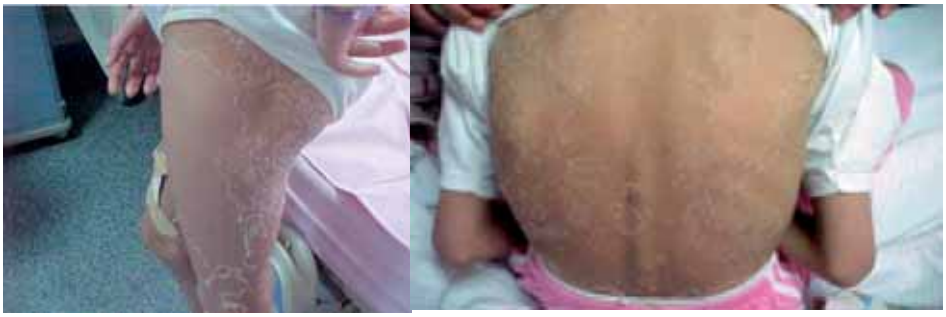

Figure 1. Skin eruption and desquamation on the trunk and leg.

sulfonamides [1,3]. Eosinophilia is present in 90% of cases, and mononucleosis occurs in 40% [4]. Clinically, DRESS is characterized by severe cutaneous eruption, lymphadenopathy, fever, and organ involvement. Systemic illness may manifest as hepatitis, arthralgia, pulmonary infiltrates, and interstitial nephritis [3].

A 13-year-old girl with chronic renal disease as a result of vesicoureteral reflux presented with a generalized rash, desquamation, and edema of the eyes and feet. She had been receiving dialysis for 7 years, trimethoprim-sulfamethoxazole for 5 years, and calcium and amino acids for 1 year. Allopurinol had been initiated 3 weeks previously. After 2 weeks of treatment with allopurinol, she was administered 4 doses of intramuscular penicillin followed by 2 days of oral penicillin because of neck pain and fever. On the third day of treatment with penicillin, generalized erythroderma and itching were noted, penicillin was discontinued, and an antihistamine was prescribed. Her skin symptoms persisted despite the discontinuation of penicillin.

On examination, she had a maculopapular rash that was more prominent on the trunk, generalized desquamation, bilateral enlarged cervical lymphadenopathy, and edema of the eyes and feet. The liver was palpable 3 cm below the right costal margin (Figure 1). Laboratory investigations showed a white cell count of 7200/µL with 6.9% eosinophils, 48% polymorphonuclear cells, 26% monocytes, and 19% lymphocytes. The total immunoglobulin (Ig) E level was 5.83 kU_A/L. Studies for viral serology were negative. Complement levels (3 and 4) were normal. The eosinophil percentage reached 40% in the third week and the liver enzymes (alanine aminotransferase and aspartate aminotransferase) increased to 220 U/L in the fourth week.

Biopsy revealed epidermal changes including spongiosis, focal parakeratosis, and basal cell vacuolization. A perivascular infiltrate composed of lymphocytes, neutrophils, and eosinophils was also noted in the superficial and deep dermis. A number of eosinophils and erythrocytes were scattered among the dermal collagen fibers (Figure 2). The patient was diagnosed as having DRESS syndrome, allopurinol was discontinued, and systemic corticosteroids and an antihistamine were started. The rash and desquamation disappeared gradually, while abnormal liver function and eosinophilia resolved in 4 to 5 weeks. The patient is now well and on continuous peritoneal dialysis.

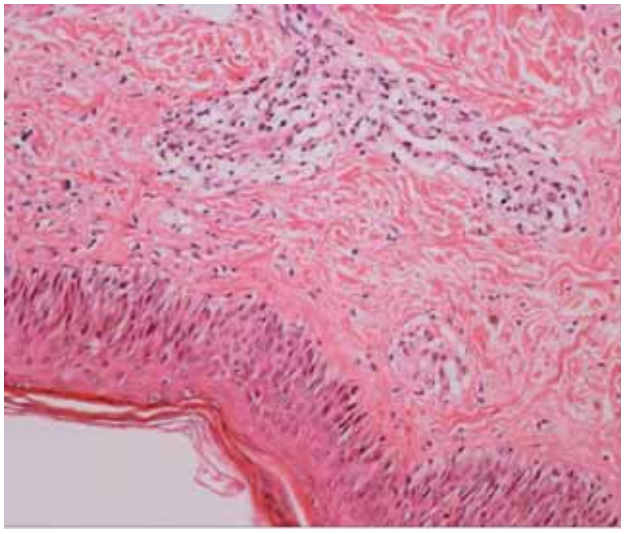

Figure 2. Skin biopsy showing epidermal changes including spongiosis, focal parakeratosis and basal cell vacuolization. A perivascular infiltrate composed of lymphocytes, neutrophils, and eosinophils was also noted in the superficial and deep dermis.

DRESS is an acute, severe, and life-threatening disease, whose clinical presentation is unlike that of common drug hypersensitivity reactions [1]. It involves multiorgan failure as a result of conditions such as hepatitis, nephritis, encephalitis, and diabetes mellitus [1,5]. Liver involvement and eosinophilia generally begin 2 to 6 weeks after the first drug is administered, that is, later than the skin reactions [2]. Prominent peripheral eosinophilia is a common finding in DRESS (40% in our patient). Rash and hepatitis may persist for several weeks after the drug is discontinued and may actually be life-threatening, with a mortality rate of about 10% [2]. Aromatic antiepileptic agents, minocycline, and allopurinol are the most frequent causes of DRESS syndrome [2]. However, even though DRESS syndrome secondary to antiepileptic agents has been reported in pediatric patients, our patient seems to be the first pediatric case of DRESS syndrome due to allopurinol.

Allopurinol is generally considered to be a safe and well-tolerated drug, but in recent years there has been an increase in

the number of allopurinol-induced hypersensitivity reactions reported. In a recent study by Halevy et al [6], allopurinol was reported to be the most frequent cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in some parts of the world. Increased prescription rates and the dose of allopurinol may be predisposing factors for the development of drug hypersensitivity reactions. The DRESS syndrome caused by allopurinol is characterized by fever, eosinophilia, and hepatitis with increased liver enzyme levels, renal failure, and rash that manifests 2 to 6 weeks after the initiation of drug treatment. Mortality rates may be as high as 20% [7,8].

Patients receiving allopurinol should be closely monitored for possible adverse reactions, and the drug should be discontinued in cases of skin or systemic reaction.

References

1. Nakashima H, Yamane K, Ihn H, Nakamura K, Watanabe R, Kuwano Y, Takekoshi T, Watanabe T, Hattori N, Fujimoto M, Tamaki K. Drug-induced hypersensitivity syndrome associated with transient hypogammaglobulinemia and increase in serum IgE level. Dermatology. 2005;210:349-52.
2. Roujeau JC, Stem R. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331:1272-85.
3. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. Toxicology. 2005;209:123-9.
4. Cameron JS, Simmonds HA. Use and abuse of allopurinol. BMJ. 1987;294:1504-5.
5. Guillon JM, Joly P, Autran B, Denis M, Akoun G, Debre P, Mayaud C. Minocycline-induced cell-mediated hypersensitivity pneumonitis. Ann Int Med. 1992;117:476-81.
6. Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidorofff A, Naldi L, Dunant A, Viboud C, Roujeau JC, Euroscar Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol 2008;58:25-32.
7. Shalom R, Rimbroth S, Rozenman D, Markel A. Allopurinol-induced recurrent DRESS syndrome: pathophysiology and treatment. Ren Fail 2008;30:327-9.
8. Callot V, Roujeau JC, Bagot M, Wechsler J, Chosidow O, Souteyrand P, Morel P, Dubertret L, Avril MF, Revuz J. Drug-induced pseudolymphoma and hypersensitivity syndrome. Two different clinical entities. Arch Dermatol. 1996;132:1315-21.

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Irritative Contact Dermatitis Due to Gentian Violet (Methylrosaniline Chloride) in an Airplane Passenger: A Case Report

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Key words: Irritative contact dermatitis. Gentian violet (methylrosaniline chloride). Patch tests. Eczematous lesions. Antiseptic therapeutic dye.

Palabras clave: Dermatitis de contacto irritativo. Cloruro de metilrosanilina (violeta de genciana). Pruebas epicutáneas. Lesiones eccematosas. Solución antiséptica terapéutica.

Most irritative contact dermatitis lesions induced by topical drugs or chemical agents develop an acute clinical course, with lesions appearing within a few hours of the first contact exposure [1]. Clinical manifestations consist of an intense erythema and blisters of different sizes. In some cases, chemical burns, crust formation, skin flaking, and subsequent epithelial repair may also occur [2].

We report the case of a 28-year-old Chinese woman, without a history of allergy, who was seen at the emergency room with erythematous, edematous, and painful purple-stained bullous lesions on the lumbar area of the back; the lesions were clinically similar to second-degree burns. She had applied an ointment containing gentian violet (methylrosaniline chloride) 3% on her back to treat nephritic colic following the advice of a Chinese naturopath a day before departing China. She reported not having taken any other drugs.

The patient had traveled from Shanghai, China to Madrid, Spain on a 14-hour-flight during which she was in contact with the gentian violet at all times. She reported the appearance of a painful burning sensation on her back during the flight. The sensation became even more intense after landing, prompting the patient to visit the hospital. The skin lesions were treated as burns and the dermatology department performed a punch biopsy of the lesions. The patient improved and remained completely asymptomatic for the next 3 weeks.

She was referred to the allergy department for more studies. Patch tests were performed with gentian violet (0.25%, 0.5%, and 2% in water; closed and open patch test), latex, and a battery of organic colorants (Marti-Tor, Barcelona, Spain) with negative results at 48 and 96 hours.

The histopathologic study revealed large intradermal spongiotic vesicles with many necrotic keratinocytes scattered around the blister area. In the superficial dermis there was an intense mixed inflammatory infiltrate mostly composed of lymphocytes with numerous neutrophils permeating the overlying epidermis (Figure). All these findings were consistent with typical eczematous lesions.

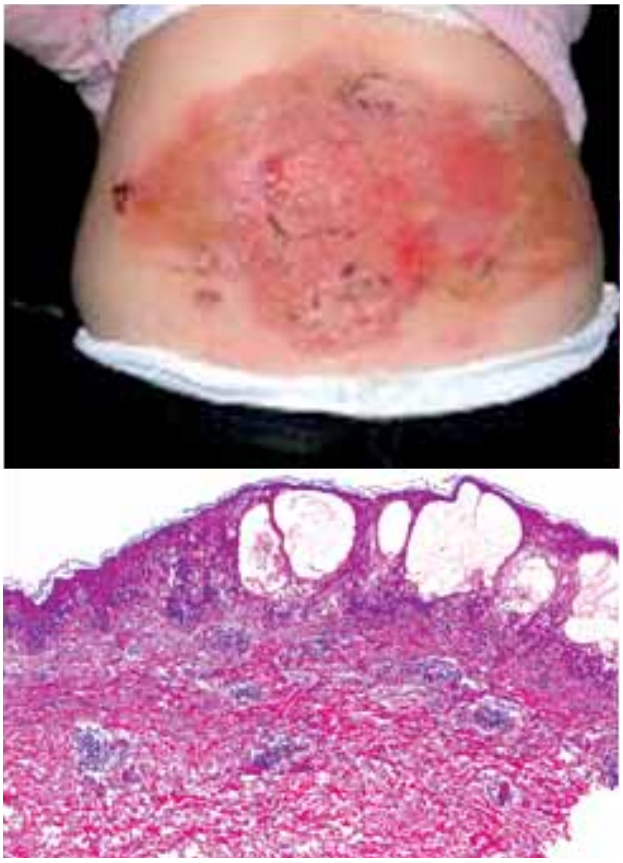

Figure. Top, intense erythema with blisters of different sizes and skin flaking on the back of the patient after the gentian violet had been removed. Bottom, histopathologic analysis of skin lesion samples obtained by punch biopsy.

The cutaneous lesions resolved completely, leaving just residual hyperpigmentation.

Triphenylmethane dyes, the best known of which are gentian violet, methyl violet, and rosaniline (basic fuchsin), are among the most used topical skin agents in Europe. They are considered weak sensitizers and there have been relatively few reports of contact sensitization to these dyes [3].

Antiseptic therapeutic dyes such as gentian violet, often used at a concentration of 0.5%, have mycostatic and antibacterial properties, which are believed to produce clinical benefits [4]. The prevalence of sensitivity to topical antibacterial agents varies from place to place and time to time in accordance with prescribing habits [5].

Although the first report on sensitization to gentian violet was published by Goldstein [6] in 1940, the author referred to a 3% gentian violet solution applied in intertriginous spaces, indicating that in all probability, this was a toxic or irritative reaction rather than an allergic one. We have presented a case of contact dermatitis in an airplane passenger who developed eczematous lesions with typical histopathologic features. Because we did not find any evidence of allergic sensitization, we also believe that an irritative or toxic mechanism was involved in its pathogenesis.

References

1. Angelini G. Topical drugs. In: Rycroft RJG, Menné T, Frich PJ (Eds). Textbook of Contact Dermatitis. 2nd ed. Berlin: Springer-Verlag, 1995:477-503.
2. Frosch PJ. Cutaneous irritation. In: Rycroft RJG, Menné T, Frich PJ (Eds). Textbook of Contact Dermatitis. 2nd ed. Berlin: Springer-Verlag, 1995.28-61.
3. Bielicky T, Novak M. Contact-Group sensitization to Triphenylmethane dyes. Arch Derm. 1969;100:540-3.
4. Schoppelrey HP, Mily H, Agathos M, Breit R. Allergic contact dermatitis from pyoctanin. Contact Dermatitis. 1997;36:221-4.
5. Bajaj AK, Gupta SC. Contact hypersensitivity to topical antibacterial agents. International Journal of Dermatology. 1986;25:103-5.
6. Goldstein MB, Sensitivity to Gentian violet. Arch Derm. 1940;41:122.

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Granulomatous cheilitis: A Condition That Merits Inclusion in the Differential Diagnosis of Angioedema

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Key words: Granulomatous cheilitis. Melkersson–Rosenthal syndrome. Angioedema. Clofazimine.

Palabras clave: Queilitis granulomatosa. Síndrome de Melkersson-Rosenthal. Angioedema. Clofazamina.

Granulomatous cheilitis was first described in 1945 by Miescher [1], although years earlier, in 1928, Melkersson had suggested a relationship between edema of the lip and facial paralysis [2]. In 1931, Rosenthal [3] added the creased tongue sign and in 1949 the triad came to be known as Melkersson-Rosenthal syndrome [4]. Recently, granulomatous cheilitis was described as part of the clinical spectrum of Crohn disease [5] and it has also been described in sarcoidosis, although more rarely [6].

Granulomatous cheilitis is clinically characterized by painless diffuse swelling of 1 or both lips. The only way to obtain a definitive diagnosis is to perform a biopsy of the

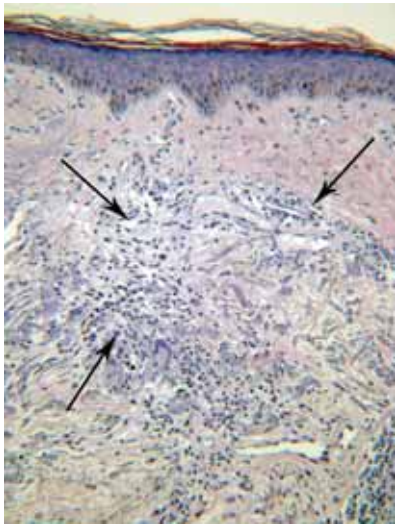

Figure. A punch biopsy specimen of the oral mucosa showing a lymphocytic crown surrounding the noncaseating granuloma (hematoxylin-eosin, original magnification ×10).

affected area. Histologically, it is characterized by noncaseating granulomatous inflammation.

We present an unusual case of granulomatous cheilitis treated successfully with clofazimine, an antileprosy agent. The aim of the present case report is to propose that granulomatous cheilitis, a condition that is often misdiagnosed, should be included in the differential diagnosis of angioedema in patients with allergic diseases.

A 44-year-old man was referred to our clinic with persistent swelling of the upper lip, without pain, pruritus, or a burning sensation. The swelling had been episodic at the beginning but had subsequently become increasingly progressive and finally persistent. His general practitioner had prescribed treatment with oral antihistamines and prednisone but there had been no clinical improvement.

Etiological agents such as food, drugs, latex, and physical and chemical factors were ruled out. There were also no reports of gastrointestinal involvement in the clinical history. The physical examination was unremarkable except for asymptomatic indurate swelling of the upper lip.

Skin prick tests with inhalant aeroallergens (Bial-Arístegui, Bilbao, Spain), food, latex, and *Anisakis simplex* were all negative. Laboratory tests (blood cell count, erythrocyte sedimentation rate, thyroid hormone profile, general biochemistry, complement, autoantibodies, urinalysis, and echinococcus and syphilis serology) and X-ray examinations were performed in order to exclude infectious diseases and gastrointestinal disorders.

Histopathologic examination revealed small non-necrotizing granulomas in the lower dermis and submucosal connective tissue, with a lymphocytic inflammatory infiltrate scattered throughout the submucosal connective tissue (Figure).

The patient was administered 100 mg of clofazimine twice daily for 3 months and the improvement was remarkable.

Although the etiology of granulomatous cheilitis is unknown, a relationship with Crohn disease has been suggested due to the granulomatous nature of the lesion [5]. Most authors, however, do not recommend routine investigations of the gastrointestinal tract in patients with a negative history of gastrointestinal complaints [5,7].

Granulomatous cheilitis is complicated to treat and spontaneous resolution and recurrence may be observed in the natural history of the disease. While the condition has been treated with many different drugs, including prednisone, minocycline, antimalarials, oral tetracycline, metronidazole, cheiloplasty, adalimumab [8], infliximab [5,9], and intralesional corticosteroids, no comparative trials have been performed to date. In the case of our patient, we would like to emphasize the good response obtained with oral clofazimine.

Clofazimine, an oral phenazine that has been used to treat leprosy for many years, has demonstrated its utility in granulomatous diseases such as granulomatous cheilitis due to its antibacterial, antiinflammatory, and immunomodulatory properties [10,11].

Adverse reactions are dose dependent and the most frequent reactions involve the skin (pigmentation, ichthyosis, and xerosis in particular), the gastrointestinal system (nausea, vomiting, and hepatotoxicity), and the eyes.

In conclusion, we would like to highlight the importance of including granulomatous cheilitis in the differential diagnosis of allergic diseases and to propose the use of a classic drug—clofazimine—to manage this difficult condition rather than 1 of the new classes of biologic agents, which will undoubtedly soon revolutionize the treatment of inflammatory disorders.

References

1. Miescher G. Über essentielle granulomatöse Makrocheilie (Cheilitis granulomatosa). Dermatologica (Basel). 1945;91:57-85.
2. Melkersson E. Ett fall av recidiverande facialispares i samband med angioneurotisk ödem. Hygiea (Stockh). 1928;90:737-41.
3. Rosenthal C. Klinisch-erbbiologischer Beitrag zur Konstitutionspathologie. Gemeinsames Auftreten von (rezidivierender familiärer) Facialislähmung, angioneurotischem Gesichtödem und Lingua plicata in Arthritismus-Familien. Z Neurol Psychiatr. 1931;131:475-500.
4. Luscher E.Melkerson Rosenthal syndrome. Schweiz Med Wochenschr. 1949; 79:1-3.
5. Ratzinger G, Sepp N, Vogetseder W, Tilg H .Cheilitis granulomatosa and Melkersson-Rosenthal syndrome: evaluation of gastrointestinal involvement and therapeutic regimens in a series of 14 patients. Journal of the European Academy of Dermatology and Venereology. 2007;21:1065-70.
6. van Maarsseveen AC, van der Waal I, Stam J, Veldhuizen RW, van der Kwast WA. Oral involvement in sarcoidosis. Int J Oral Surg. 1982;11:21-9.
7. van der Waal RI, Schulten EA, van der Meij EH, van de Scheur MR, Starink TM, van der Waal I. Cheilitis Granulomatosa: overview of 13 patients with long-term follow-up-results of management. International Journal of Dermatology. 2002;41:225-9.
8. Kakimoto C, Sparks C, White AA. Melkersson-Rosenthal syndrome: a form of pseudoangioedema. Ann Allergy Asthma Immunol. 2007 Aug;99(2):185-9.
9. Barry O, Barry J, Langan S, Murphy M, Fitzgabbon J, Lyons

JF. Treatment of granulomatous cheilitis with infliximab. Arch Dermatol 2005;141:1080-2.
10. Fdez-Freire LR, Serrano Gotarredona A, Bernabeu Wittel J, Pulpillo Ruiz A, Cabrera R, Navarrete Ortega M, Conejo-Mir J. Clofazamine as elective treatment for granulomatous cheilitis. J Drugs Dermatol. 2005 May-Jun;4(3):374-7.
11. Ridder GJ, Frandis M, Lohle E. Cheilitis granulomatosa Miescher: treatment with clofazimine and review of the literature. Ann Otol Rhinol Laryngol. 2001;110:964-7.

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Discordant Positive Results of Multiallergen Immunoglobulin E Tests in Relation to Cross-Reactive Carbohydrate Determinants and Alcohol Consumption

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Key words: IgE. Cross-reactive carbohydrates. Multiallergen tests. Alcohol.

Palabras clave: IgE. Carbohidratos con reactividad cruzada. Tests multialergeno. Alcohol.

Cross-reactive carbohydrate determinants (CCDs) are N-glycans in plant and invertebrate glycoproteins that interfere with the in vitro diagnosis of allergy by inducing widespread immunoglobulin (Ig) E reactivity [1-3]. Significant levels of specific IgE (sIgE) to CCDs are present in about 5% of the adult population [4]. Prevalence is higher in individuals being studied for respiratory allergy [5] and in heavy drinkers [4]. It has been asserted that the risk of CCD interference with IgE determinations increases if several products are mixed in the same reagent [3], as occurs with the multiallergen IgE tests (MT) used to diagnose allergy. However, this interference has not been entirely proven. In an earlier study [6], we observed that the excess MT positivity observed in heavy drinkers was related to CCD reactivity, but we did not perform skin prick tests (SPT). In the present study, we investigated the serum levels of IgE to CCD in a general adult population stratified according to the results of SPT and MT.

Our data were from an adult population-based survey in A Estrada, Spain [7]. Previous reports about this population have included the results of MT (UniCAP Phadiatop, Phadia, Sweden) [8], SPT to mites, pollens, molds, and animal dander (ALK-Abelló, Madrid, Spain) [9], and sIgE to a CCD (MUXF^3 [Ro214], the N-glycan from bromelain, Phadia) [4]. The 457 individuals were classified into 4 groups as follows: MT-negative and SPT-negative; MT-negative and SPT-positive; MT-positive and SPT-negative; and MT-positive and SPT-positive. The MT result was defined as positive or negative following the manufacturer's instructions. SPT were considered positive when the wheal produced by the reaction to any of the 13 allergens tested was at least 4 mm in diameter. Study participants were classified as symptomatic if they answered "yes" to either of the following questions: "Have you ever had a problem with sneezing, or a runny or blocked nose when you did not have a cold or the flu?" and "Have you ever had wheezing or whistling in the chest at any time in the past?" [8].

The highest levels of sIgE to CCD were found among individuals with positive MT and negative SPT results (discordant positive MT)—more than 50% showed levels of at least 0.35 kU$_A$/L (Figure). Nine of 31 individuals (29%) with discordant positive MT were heavy drinkers (weekly alcohol intake >28 units/week). Discordant positive MT was found

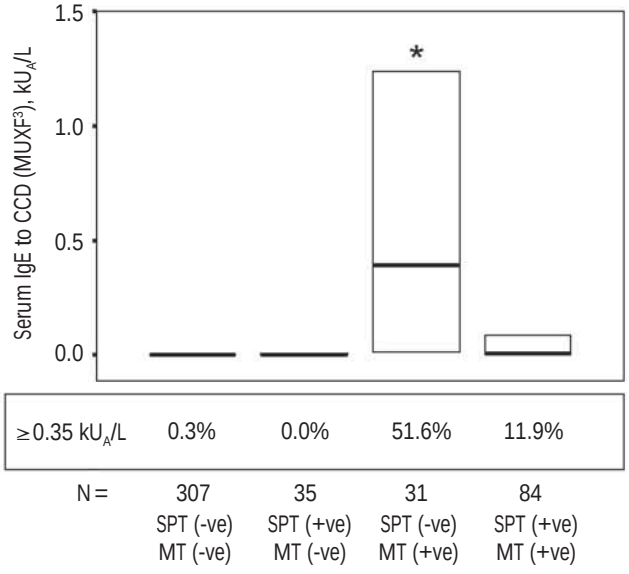

Figure. Serum levels of IgE to CCD (MUXF^3) in the general adult population stratified according to the results of skin prick tests (SPT) and multiallergen IgE tests (MT). Boxes represent the interquartile range. Horizontal solid lines represent median values. Numbers at the bottom of the bars represent the percentage of individuals with levels of CCD-sIgE ≥0.35 kU$_A$/L in each group. +ve indicates positive; -ve, negative.
*P < .001 with respect to every other group (Mann-Whitney test).

in 13 of 218 (6%) abstainers/occasional drinkers, 9 of 195 (5%) moderate drinkers (1-28 units/week), and 9 of 44 (21%) heavy drinkers ($P = .001$, χ^2 test). In the logistic regression analysis, discordant positive MT was associated with heavy drinking after adjusting for age, sex, and smoking (odds ratio 3.6; 95% CI, 1.2-11.1, $P = .02$; reference category, abstainers). Twelve of the 31 individuals (39%) with discordant positive MT were symptomatic. This proportion was similar to that of individuals with negative MT and negative SPT (130 of 307, 42%, $P = .84$), and lower than that of individuals with positive MT and positive SPT (61 of 84, 73%; $P = .001$, χ^2 test).

Our results are consistent with those of other authors [1-3], who show that CCDs interfere with in vitro diagnostic tests and show little activity in vivo, since patients with this IgE do not have symptoms when they are exposed to CCDs. This contrasts with in vitro biologic activity, as the basophils of patients with IgE against CCDs are activated when exposed to CCDs [1]. This discrepancy may be due to the presence of tolerogenic IgG antibodies [1]. Furthermore, our results extend previous reports indicating that CCD interference is frequent in heavy drinkers [4]. Interference is of particular importance in the case of MTs, which are commonly used as screening tools in settings where SPT are not readily available.[10] The results of MTs should be interpreted with caution in groups in which CCD are prevalent (eg, heavy drinkers).

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References

1. Altmann F. The role of protein glycosylation in allergy. Int Arch Allergy Immunol. 2007;142:99-115.
2. van Ree R. Carbohydrate epitopes and their relevance for the diagnosis and treatment of allergic diseases. Int Arch Allergy Immunol. 2002;129:189-97.
3. Malandain H. IgE-reactive carbohydrate epitopes--classification, cross-reactivity, and clinical impact (2nd part). Eur Ann Allergy Clin Immunol. 2005;37:247-56.
4. González-Quintela A, Garrido M, Gude F, Campos J, Linneberg A, Lojo S, Vidal C. Sensitization to cross-reactive carbohydrate determinants in relation to alcohol consumption. Clin Exp Allergy. 2008;38:152-60.
5. Mari A. IgE to cross-reactive carbohydrate determinants: analysis of the distribution and appraisal of the in vivo and in vitro reactivity. Int Arch Allergy Immunol. 2002;129:286-95.
6. Coutinho V, Vidal C, Garrido M, Gude F, Lojo S, Linneberg A, González-Quintela A. Interference of cross-reactive carbohydrates in the determinations of specific IgE in alcohol drinkers and strategies to minimize it: the example of latex. Ann Allergy Asthma Immunol. 2008;101:394-401.
7. González-Quintela A, Gude F, Boquete O, Rey J, Meijide LM, Suárez F, Fernández-Merino MC, Pérez LF, Vidal C. Association of alcohol consumption with total serum immunoglobulin E levels and allergic sensitization in an adult population-based survey. Clin Exp Allergy. 2003;33:199-205.
8. Vidal C, Gude F, Boquete O, Fernández-Merino MC, Meijide LM, Rey J, Lojo S, González-Quintela A. Evaluation of the Phadiatop test in the diagnosis of allergic sensitization in a general adult population. J Invest Allergol Clin Immunol. 2005;15:124-30.
9. Vidal C, Boquete O, Gude F, Rey J, Meijide LM, Fernández-Merino MC, González-Quintela A. High prevalence of storage mite sensitization in a general adult population. Allergy. 2004;59:401-5.
10. Linneberg A, Hertzum I, Husemoen LL, Johansen N, Jorgensen T. Association between alcohol consumption and aeroallergen sensitization in Danish adults. Clin Exp Allergy. 2006;36:714-721.

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Bird-Egg Syndrome Caused by *Agapornis* Species (Lovebird)

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Key words: Agapornis. Alpha-livetin. Asthma. Bird-egg syndrome. Feathers.

Palabras clave: Agapornis. Alfalivetina. Asma. Síndrome ave-huevo. Plumas.

The allergic manifestations of sensitization to bird allergen (feathers, droppings, serum) may appear as the bird-egg syndrome, with respiratory symptoms induced by bird antigens and gastrointestinal symptoms after intake of bird egg. These symptoms are generally caused by sensitization to bird alpha-livetin (serum albumin) [1-4].

The lovebird (genus *Agapornis*) is a very social parrot that is often kept as a pet. We have found no reported cases of bird-egg syndrome caused by sensitization to lovebird allergen.

A 38-year-old nonatopic woman who was an ex-smoker consulted with a 2-year history of persistent rhinitis and several episodes of nocturnal dry cough, dyspnea, and wheezing. During the previous 5 months, she had experienced abdominal pain when she ate fried chicken egg, although she tolerated well-cooked chicken egg and chicken meat. She had kept 2 lovebirds as pets for the previous 6 years.

Baseline spirometry and chest x-ray were normal. Skin prick tests with commercial aeroallergens and foods (ALK-Abelló SA, Madrid, Spain) were positive to pollens (grass, mugwort, *Parietaria judaica*), feathers (canary, budgerigar, duck, chicken), chicken egg and its fractions (yolk, white, ovalbumin, and ovomucoid), and sunflower seeds.

Prick test results were positive to lovebird feathers (1% w/v) and droppings (10% w/v) (the widest wheals were 10 mm and 9 mm, respectively, in diameter), chicken egg (raw yolk 18 mm, raw white 18 mm, cooked white 6 mm), and chicken meat (10 mm), but they were negative to cooked egg yolk.

The patient removed the birds from her home and was asymptomatic 4 months later. The methacholine inhalation test revealed no bronchial hyperresponsiveness (concentration causing a 20% decrease in forced expiratory volume in 1 second [PC_{20}] >16 mg/mL), the fraction of exhaled nitric oxide (FE_{NO}) was 19 ppb, and the differential cell count of induced sputum at baseline conditions showed no eosinophils. Specific inhalation challenge (SIC) was carried out by the tidal breathing method through a De Vilbiss model 646 nebulizer with an aqueous extract of lovebird feathers at 7.5 mg/mL and elicited a dual asthmatic response, with maximum decreases in forced expiratory volume in 1 second (FEV_1) from baseline of 23% and 31%, respectively. Twenty-four hours after SIC, the methacholine test showed a significant variation with respect to the baseline value (PC_{20} 0.5 mg/mL), the FE_{NO} was 33 ppb, and the differential cell count of the induced sputum showed an increase in eosinophils of up to 25%.

Total serum immunoglobulin (Ig) E was 591 IU/mL. Determinations of serum-specific IgE (Phadia CAP system, Uppsala, Sweden) were positive to chicken egg (yolk 19.4 kU_A/L, white 6.7 kU_A/L). Specific IgE to bird feather extract and alpha-livetin was measured by the enzyme allergosorbent test (EAST) (HYTEC Specific IgE EIA, HYCOR Biomedical Ltd, UK). The solid-phase was obtained by coupling the extract solution (10 mg/mL) or alpha-livetin (1 mg/mL) to the 6-mm CNB-activated paper discs as described by Ceska and Lunqvist [5]. EAST was performed and the results expressed in accordance with the manufacturer's instructions. Specific IgE (EAST) was positive to lovebird (> 100 kU_A/L), chicken (54.7 kU_A/L), pigeon (18.8 kU_A/L), budgerigar (16.2 kU_A/L), canary (10.1 kU_A/L), and duck feathers (2.7 kU_A/L), as well as to chicken alpha-livetin (54 kU_A/L). Sodium dodecyl sulfate polyacrylamide gel electrophoresis immunoblotting with feather extracts from different bird species revealed IgE binding bands (lovebird 132, 81, and 66 kDa; chicken 142, 97, and 69 kDa; pigeon 68 kDa; and budgerigar 167 and 94 kDa) (Figure, I). Immunoblotting inhibition studies were carried out with chicken feathers as the solid phase. When the patient's serum was preincubated with lovebird feather extract or alpha-livetin, all IgE-binding bands disappeared (Figure, II).

Our patient developed IgE-mediated rhinitis and asthma due to sensitization to the lovebird antigens contained in the feathers of her pet. Furthermore, this sensitization led to food allergy symptoms after the ingestion of slightly cooked chicken egg. The immunological results point to alpha-livetin as the responsible allergen.

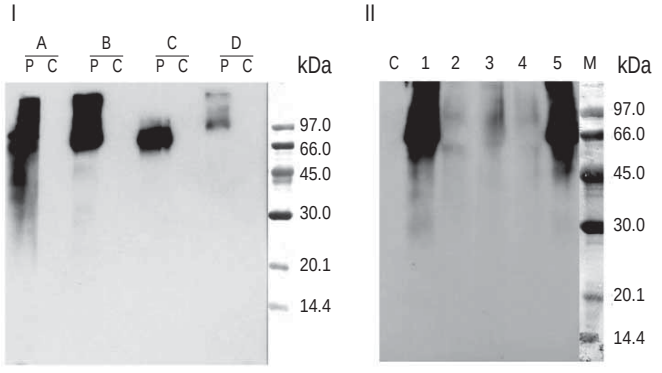

Figure. Sensitization to alpha-livetin was detected in a patient with allergic symptoms who kept lovebirds as pets. I, SDS-PAGE immunoblotting results for feather extracts from lovebird (A), chicken (B), pigeon (C) and budgerigar (D). Lane P, Patient's serum; Lane C, control serum (pool of sera from nonatopic subjects); Lane M, molecular mass marker. II, immunoglobulin E immunoblotting inhibition results using chicken feather extract as the solid phase. Lanes 1 to 5: patient serum (lane 1), patient serum preincubated with extracts of chicken feathers (lane 2), lovebird feathers (lane 3), patient serum preincubated with chicken alpha-livetin (lane 4), and lamb meat (lane 5). SDS-PAGE indicates sodium dodecyl sulfate polyacrylamide gel electrophoresis.

References

1. de Maat-BleekerF, van Dijk AG, Berrens L. Allergy to egg yolk possibly induced by sensitization to bird serum antigens. Ann Allergy. 1985;54(3):245-8.
2. Mandallaz MM, de Weck AL, Dahinden CA. Bird-egg syndrome. Cross-reactivity between bird antigens and egg-yolk livetins in IgE-mediated hypersensitivity. Int Arch Allergy Appl Immunol. 1988;87:143-50.
3. Szepfalusi Z, Ebner C, Pandjaitan R, Orlicek F, Scheiner O, Boltz-Nitulescu G, Kraft D, Ebner H. Egg yolk a-livetin (chicken serum albumin) is a cross-reactive allergen in the bird-egg syndrome. J Allergy Clin Immunol. 1994;93:932-42.
4. Quirce S, Marañón F, Umpiérrez A, de las Heras M, Fernández-Caldas E, Sastre J. Chicken serum albumin (Gal d 5) is a partially heat-labile inhalant and food allergen implicated in the bird-egg syndrome. Allergy. 2001;56:754-62.
5. Ceska M, Lundqvist U. A new and simple radioimmunoassay method for the determination of IgE. Immunochemistry. 1972;9:102-5.

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Correlation Between Total Annual Atmospheric Pollen Counts for Chenopodiaceae – Amaranthaceae and the Prevalence of Positive Skin Prick Tests to Chenopodium and/or Salsola Pollen Extracts: A Multicenter Study

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Key words: Pollen allergy. Pollen counts. Chenopodium. Salsola.

Palabras clave: Aerobiología. Alergia a polen. Contajes de polen. Chenopodium. Salsola.

The Chenopodiaceae–Amaranthaceae family belongs to the Centrospermae or Caryophyllales order, which includes more than 8000 species. Pollens from the Chenopodiaceae family have been considered among the causes of respiratory allergy since Lamson and Watry described the first cases in Arizona in 1933 [1]. The prevalence of sensitization to Chenopodiaceae in patients with hay fever symptoms is between 30% and 40% in the Iberian Peninsula [2,3].

The main objective of this study was to determine whether Chenopodiaceae sensitization in hay fever patients in Spain was primarily due to exposure to airborne pollen. To this end, we studied the correlation between the prevalence of positive skin prick tests to *Chenopodium* and/or *Salsola* in hay fever patients in 12 different geographical areas of Spain and total annual pollen counts for Chenopodiaceae–Amaranthaceae.

Pollen counts were performed following a previously described technique [4] using Burkard traps (Burkard Manufacturing Co., Rickmansworth, Hertfordshire, UK). The sampling period was from January 2000 to the end of December 2003. Thirteen cities participated in the study: Badajoz, Barcelona, Bilbao, Burgos, Ciudad Real, La Coruña, Logroño, Madrid, Santander, Seville, Toledo, Vitoria, and Zaragoza.

We determined the percentage of positive skin tests to common aeroallergens in series of consecutive patients that attended the participating clinics in each of cities between 2002 and 2003; 100 patients were enrolled in each city except in Madrid and Ciudad Real, where 236 and 200 were enrolled, respectively. Patients were selected on the basis of a history of seasonal or perennial rhinitis or asthma. We enrolled 1536 patients in total (48% men, 52% women), all of whom had been born in and were still living in or around the study city.

All the patients were skin tested (prick test) with a standardized, commercially available battery of aeroallergens at 50 histamine equivalent prick units (Inmunotek Lab., Madrid, Spain). The pollens included *Chenopodium album, Salsola kali*, and a further 25 species that we considered to be most representative of the atmosphere in the 13 geographical areas studied.

Statistical analyses were performed with the SPSS/PC software package, version 4 (SPSS Inc., Chicago, Illinois, USA). Pearson's correlation coefficient was used to correlate

Table. Presence of Airborne Pollen and Skin Test Positivity to Chenopodiaceae

	Chenopodiaceae-Amaranthaceae Pollen Counts				Positive Skin Prick Tests, %		
	2000-2003[a]	2003					
City	Annual Total Grains/m³	Annual Total Grains/m³	Peak Concentration, Grains/m³ (mm-dd-yy)	% of Total Pollen	*Chenopodium*	*Salsola*	*Chenopodium* and/or *Salsola*
Toledo	1521	1803	52 (8-28-03)	3.5	50	40	58
Zaragoza	1047	922	35 (8-29-03)	4.6	43	40	50
Ciudad Real	583	631	22 (9-22-03)	2	44	42	52
Barcelona	666	564	40 (8-29-03)	1.5	11	11	19
Seville	596	449	22 (4-28-03)	1.2	21	13	26
Madrid	379	302	12 (8-04-03)	0.9	30	35	39
Badajoz	260	274	16 (9-15-03	1	33	10	34
Burgos	146	223	9 (5-28-03)	1.7	27	18	31
Bilbao	130	152	7 (8-19-03)	0.9	14	14	16
Vitoria	65	91	12 (6-3-03)	0.3	12	11	16
Santander	17	14	5 (8-12-03)	1	4	2	5
La Coruña	7	10	2 (6-9-03)	1.6	15	15	20
Logroño	Not done	Not done	Not done		31	28	37
Average	451	453	19	1.6	26	21	31

[a] Data are presented as mean values for the 4 years.

the quantity of Chenopodiaceae–Amaranthaceae pollens collected at each station with the prevalence of positive skin tests to these pollens in the patients from each region. The Table shows the total annual pollen counts for Chenopodiaceae-Amaranthaceae.

Sensitization to Chenopodiaceae was found in 555 patients (60% women, 40% men) and only a few patients were monosensitized (between 0% and 5% depending on the region). The prevalence of asthma in the global study population was 41% as opposed to just 20% in the 555 patients sensitized to Chenopodiaceae. The details of the prevalence of positive skin tests to Chenopodiaceae–Amaranthaceae pollens in each region are presented in the Table.

There was a statistically significant correlation between the annual atmospheric pollen counts for Chenopodiaceae–Amaranthaceae and the prevalence of positive skin prick tests to *Chenopodium* and/or *Salsola* pollen extracts ($r = 0.78$, $P = .002$).

In conclusion, we found that airborne Chenopodiaceae–Amaranthaceae pollens were present, albeit at low levels, in all the regions studied. Although these pollens accounted for just 1.6% of all pollen collected, the mean prevalence of positive skin tests in hay fever patients was high (31%), occupying third place with regard to pollen sensitization after grass and olive pollens (data not shown) in this multicenter study.

Finally, we found a positive correlation between the prevalence of sensitization to Chenopodiaceae pollen and total annual Chenopodiaceae-Amaranthaceae pollen counts. This would suggest that the sensitization observed in this study was principally due to a true sensitization to airborne Chenopodiaceae pollen rather than to cross-reactivity [5-7] with other taxonomically unrelated pollens and/or foods.

References

1. Lamson W, Watry A. The importance of the Chenopodiaceae in pollinosis: with special reference to Winslow and Holbrook, Arizona. J. Allergy. 1933;4:255-281.
2. Pola J. Alergia a pólenes de Quenopodiáceas. Rev. Esp. Alergol Inmunol Clin. 2003;18:39-44.
3. Galán C, Infante F, Ruiz de Clavijo E, Guerra F, Miguel R, Domínguez E. Allergy to pollen grains from Amaranthaceae and Chenopodiaceae in Cordoba, Spain. Annual and daily variation of pollen concentration. Annals of Allergy. 1989;63(11):435-38.
4. Jäger S. Recommendations for methodology for routinely performed monitoring of airborne pollen. Practical Workshop II: Collection and identification of pollens. In "Syllabus" of Postgraduate courses and practical workshop (XVI ECACI' 95, Madrid). Torrent (Valencia): Basomba A., Sastre J. 1995: 329-30.
5. Lombardero M, Duffort O, Selle´s JG, Hernandez J, Carreira J. Crossreactivity among Chenopodiaceae and Amaranthaceae. Ann Allergy. 1985;54:430-6.
6. Florido JF, Quiralte J, Saenz de San Pedro B, Bartolome B. Crossreactivity between Olea europaea and Chenopodium album pollens. Allergy. 2000;55(supl 63):158.
7. Van Ree R, Voitenko V, Van Leeuwen WA, Aalberse RC. Profilin is a cross-reactive allergen in pollen and vegetable foods. Int Arch Allergy Immunol. 1992;98:97-104.

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Urticaria Caused by Pentoxifylline

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Key words: Oral challenge. Pentoxifylline. Urticaria. Xanthines.

Palabras clave: Provocación oral. Pentoxifilina. Urticaria. Xantinas.

Purines include adenine, guanine, 6-methylaminopurine and xanthines. Pentoxifylline is a dimethyl-substituted xanthine with similar properties to other xanthine derivatives such as theobromine, caffeine, and theophylline. While purine-induced allergic reactions are rare, those caused by pentoxifylline in particular are extremely rare.

We report the case of a 29-year-old woman without a history of atopy who initiated treatment with pentoxifylline prescribed by her general practitioner to treat a vascular disorder. Clinical symptoms, which included itching of the chin, erythema of the palms, and isolated pruritic hives on the breasts, buttocks, and back, appeared 20 minutes after intake of the first dose. There were no signs or symptoms of an anaphylactic reaction. Skin lesions disappeared within an hour in the absence of treatment. The patient did not remember having taken pentoxifylline previously.

After providing written informed consent, the patient underwent skin tests with a commercial parenteral preparation of pentoxifylline; both the prick test (20 mg/mL) and intradermal test (0.2 mg/mL) were negative. One month after the episode, a single-blind, placebo-controlled oral challenge study was performed with a xanthine (theophylline), a structural analogue of hypoxanthine (allopurinol), and pentoxifylline (Figure). Challenges were negative for theophylline and allopurinol up to therapeutic doses; 20 minutes after receiving 400 mg of pentoxifylline (cumulative dose, 600 mg), the patient complained of pruritus of the chin and presented pruriginous erythematous papule lesions near the areola and on the back and buttocks. These symptoms were alleviated following treatment with methylprednisolone and dexchlorpheniramine.

Pentoxifylline, which is widely used for the treatment of various types of vascular disorders, has hemorheological properties, thought to be due to the drug's ability to reduce

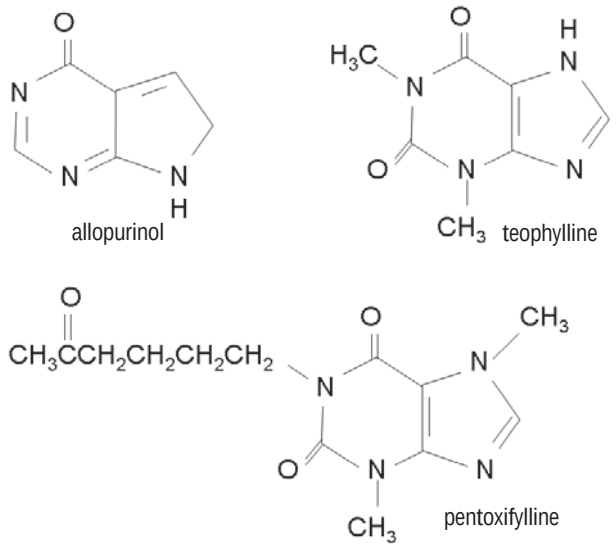

Figure. Chemical structure of tested drugs.

blood viscosity and increase the filterability of blood cells [1]. It has also been used to treat other disorders, mainly cutaneous diseases, thanks to its antiinflammatory and immunomodulatory properties [2].

In 2005, 9438 packages of pentoxifylline were consumed in our health care district, which serves a population of 390 000 inhabitants. Allergic reactions induced by xanthines are rare [3,4,5] and our review of the literature revealed just one report of urticaria induced by pentoxifylline [6].

We have reported a case of allergic reaction due to pentoxifylline confirmed by challenge test. Clinical cross-reactivity with other xanthines (in this case theophylline) and a structural analogue of hypoxanthine (allopurinol) was ruled out. Although the clinical presentation was compatible with an immediate hypersensitivity reaction, we were unable to detect pentoxifylline-specific immunoglobulin E by skin testing. The only useful method for confirming diagnosis in our case was a controlled challenge study.

References

1. Ward A, Clissold S. Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. Drug.1987;34:50-97.
2. Wolf R, Matz H, Orion E, Tuzun B, Tuzun Y. Miscellaneous treatments, I: sulfasalazine and pentoxifylline: unapproved uses, dosages, or indications. Clinics in Dermatology. 2002;20:531-46.
3. Hinrichs R, Hunzelmann N, Ritzkowsky A., Zollner TM, Krieg T, Scharffetter-Kochanek K. Caffeine hypersensitivity. Allergy. 2002;57:859-60.
4. Infante S, Baeza ML, Calvo M, De Barrio M, Rubio M, Herrero T. Anaphylaxis due to caffeine. Allergy. 2003;58:681–2.
5. Fernández-Nieto M, Sastre J, Quince S. Urticaria caused by cola drink. Allergy. 2002;57:967-8.
6. Gonzalez-Mahave I, Del Pozo MD, Blasco A, Lobera T, Venturini M. Urticaria due to pentoxifylline. Allergy. 2005;60:705.

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Asthmatic Reaction Induced by Celecoxib in a Patient With Aspirin-Induced Asthma

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Key words: Aspirin. Asthma. Celecoxib. NSAID intolerance. Oral challenge.

Palabras clave: Aspirina. Asma. Celecoxib. Intolerancia a AINEs. Test de provocación.

Selective cyclooxygenase-2 (COX-2) inhibitors are an alternative to nonsteroidal anti-inflammatory drugs (NSAIDs) for patients who experience cutaneous or respiratory symptoms after taking these drugs (intolerance to NSAIDs). The safety of celecoxib and other COX-2 inhibitors has been demonstrated in various studies, and patients with NSAIDs-related respiratory symptoms tolerate it better than patients with cutaneous ones [1,2].

We present the case of a 25-year-old woman diagnosed with brittle asthma and allergic rhinoconjunctivitis who was sensitized to dust mite and dog dander (positive skin prick test and RAST results: *Dermatophagoides pteronyssinus*, 9.02 kU_A/L; *Dermatophagoides farinae*, 5.18 kU_A/L; dog dander, 2.24 kU_A/L). Formoterol/budesonide 9/640 µg, montelukast 10 mg, ebastine 20 mg, and intranasal mometasone furoate constituted her usual treatment regimen. She had presented anaphylactic reactions to tomato, shrimp, and melon with positive skin prick test results to all these foods. She reported 3 episodes of bronchospasm precipitated by diclophenac and 1 by metamizole. She tolerated 650 mg of paracetamol. With the clinical diagnosis of aspirin-induced asthma, an oral challenge with celecoxib was conducted to provide her with an alternative analgesic drug. Inhaled corticosteroids and long-acting $ß_2$-adrenergic agonists were continued, but montelukast was discontinued 5 days before the challenge procedure. Physical examination and lung function were normal at baseline. Due to the presence of brittle asthma, a slow oral challenge schedule was planned, and 20 mg, 100 mg, and 100 mg of celecoxib were administered at 1-hour intervals. Ten minutes after taking 20 mg of celecoxib,

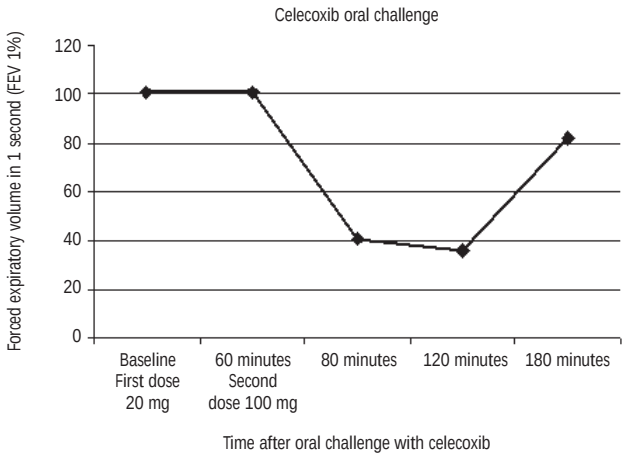

Figure. Oral challenge with celecoxib.

she complained of itching on the roof of her mouth, although there was no change in lung function. Oral challenge was continued, and 20 minutes after taking 100 mg of celecoxib, she presented severe dyspnea with a significant fall in lung function (Figure). Oxygen, short-acting ß$_2$-adrenergic agonists, intramuscular corticosteroids, and adrenaline were required to recover the lung function.

All series studied until 2006 showed tolerance to celecoxib in almost all NSAID-intolerant patients who presented respiratory symptoms and in 90%-100% of those with cutaneous symptoms [1,2]. The first case of bronchospasm with celecoxib was observed in an asthmatic patient in 2006 (at a dose of 15 mg) [3], and, since then, only 1 case has been described [4]. A rofecoxib-related bronchospasm was reported in 2006 [5] and an asthma attack precipitated by etoricoxib [6] was reported earlier this year (2008). We report the third celecoxib-induced asthma attack. All previously reported patients were nonatopic, except the patient who reacted to etoricoxib (RAST result of 0.63 kU$_A$/L for *D pteronyssinus*). The patient who died from rofecoxib-induced severe bronchospasm had a history of food allergy and sensitization to dust mite and mold. However, neither skin prick test nor RAST results were provided. Our patient is the first case of very severe bronchospasm (64% fall in forced expiratory volume in 1 second) due to celecoxib in an atopic patient (allergic rhinitis and food allergy).

Although COX-2 inhibitors have an excellent safety profile, our study shows that an oral challenge in patients with aspirin-induced asthma is still mandatory.

References

1. Dahlén B, Szczeklik A, Murray JJ; Celecoxib in Aspirin-Intolerant Asthma Study Group. Celecoxib in patients with asthma and aspirin intolerance. The Celecoxib in Aspirin-Intolerant Asthma Study Group. N Engl J Med. 2001;11;344(2):142.
2. Valero A, Enrique E, Baltasar M, Cisteró A, Martí E, Picado C. Celecoxib en pacientes con reacciones adversas cutáneas y respiratorias a los antiinflamatorios no esteroideos. Med Clin (Barc). 2003;121:695-6.
3. Baldassare S, Schadene L, Choufani G, Michils A. Asthma attacks induced by low doses of celecoxib, aspirin, and acetaminophen. J Allergy Clin Immunol. 2006;117:215-7.
4. Mastalerz L, Sanak M, Gawlewicz A, Gielicz A, Faber J, Szczeklik A. Different eicosanoid profile of the hypersensitivity reactions triggered by aspirin and celecoxib in a patient with sinusitis, asthma, and urticaria. J Allergy Clin Immunol. 2006;118(4):957-8.
5. Titchen T, Cranswick N, Beggs S. Adverse drug reaction to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital. Br J Clin Pharmacol. 2005;59:718-23.
6. Koschel D, Cardoso C, Leucht V, Hoffken G. Asthmatic reaction induced by etoricoxib in a patient with aspirin-sensitive asthma. Allergy. 2008;63:1087-94.

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Hypersensitivity Reaction to Omeprazole in a Child

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Key words: Proton pump inhibitors. Acid-peptic disorders. Omeprazole. Hypersensitivity. Child. Anaphylaxis.

Palabras clave: Inhibidores de la bomba de protones. Omeprazol. Hipersensibilidad. Niño. Anafilaxia.

Proton pump inhibitors are the most potent inhibitors of gastric acid secretion. The proton pump inhibitor, omeprazole, and related drugs are used in the treatment of acid-peptic disorders in adults and children [1]. However, anaphylactic reactions due to omeprazole have rarely been described in adults [2-5] and, in children, there have been no reported cases of anaphylactic reaction due to omeprazole to date.

A 14-year-old boy was admitted to our pediatric emergency department with generalized itching, diffuse erythema, facial edema, severe dyspnea, and decreased level of consciousness. Physical examination revealed wheezing, perioral cyanosis, diffuse rhonchi and fine crackles, widespread urticaria, and angioedema of the face. His vital signs included a respiratory rate of 30 breaths/min, a heart rate of 120 beats/min, and low

blood pressure (50/30 mm Hg). An acute anaphylactic reaction was diagnosed and treated with intramuscular epinephrine, intravenous diphenhydramine, methylprednisolone, fluid expansion, nebulized albuterol, and oxygen therapy. Over the next 3 hours, his vital signs and level of consciousness returned to normal.

He had undergone gastroscopy for persistent dyspeptic complaints 2 days prior to the reaction. The process revealed gastritis and an antral ulcer with negative cultures for *Helicobacter pylori*. Therefore, he was prescribed only oral omeprazole at 20 mg once daily. The anaphylactic reaction began 2 hours after the first dose. The patient had no personal or family history of atopic disease or other drug sensitivity and he was not taking any concomitant therapy at the time of the reaction. His parents claimed that, 2 months previously, he had received a 7-day course of omeprazole for dyspeptic complaints. Before discharge, we determined total immunoglobulin (Ig) E, which was normal (60 IU/mL). We could not perform specific IgE testing for omeprazole. One month after the reaction, we performed skin prick tests with omeprazole (Losec® IV, AstraZeneca Ltd, Luton, UK) and lansoprazole (Lansor, Sanovel Ltd, Silivri, Turkey), and the results were negative. Thus, we performed intradermal tests with omeprazole at a concentration of 4 mg/mL and lansoprazole at a concentration of 30 mg/mL in normal saline. The results of both were positive (wheal 12 × 10 mm and 8 × 7 mm, respectively, with erythema) [3]. Therefore, we applied skin prick testing to establish hypersensitivity to omeprazole and lansoprazole. We also carried out skin prick testing with common inhalant allergens and foods, although the results were negative**.** The results were considered positive if a wheal of at least 3 mm or greater than that of the saline control was obtained, and if it was surrounded by a flare. We confirmed that hypersensitivity to omeprazole was responsible for this anaphylactic reaction.

Immediate-type hypersensitivity reactions induced by omeprazole and other proton pump inhibitors are rare [2], although the incidence of adverse events due to omeprazole is low [2,3]. There are few reports of omeprazole-induced anaphylaxis after oral or intravenous administration [2-5] in adult patients, but, to date, there have been no reported cases in children.

Skin tests were performed in all the reported adult cases and proved to be effective for diagnosing hypersensitivity to proton pump inhibitors [3,4], although specific serum IgE could not be measured in vitro using radioimmunoassay [3] or radioallergosorbent tests [4]. Therefore, we performed skin tests to confirm hypersensitivity and these elicited a positive reaction to omeprazole.

To our knowledge, this is the first report of omeprazole-induced anaphylaxis in a child. Given that children with no previous documented allergy to proton pump inhibitors can experience an anaphylactic reaction to omeprazole—albeit a rare occurrence—pediatricians should exercise caution when prescribing this drug.

References

1. Jain KS, Shah AK, Bariwal J, Shelke SM, Kale AP, Jagtap JR, Bhosale AV. Recent advances in proton pump inhibitors and management of acid-peptic disorders. Bioorg Med Chem. 2007,1;15:1181-205.
2. Confino-Cohen R, Goldberg A. Anaphylaxis to omeprazole: diagnosis and desensitization protocol. Ann Allergy Asthma Immunol. 2006;96:33-6.
3. Galindo PA, Borja J, Feo F, Gómez E, García R, Cabrera M, Martínez C. Anaphylaxis to omeprazole. Ann Allergy Asthma Immunol. 1999;82:52-4.
4. González P, Soriano V, López P, Niveiro E. Anaphylaxis to proton pump inhibitors. Allergol Immunopathol (Madr). 2002;30:342-3.
5. Ottervanger JP, Phaff RA, Vermeulen EG, Stricker BH. Anaphylaxis to omeprazole. J Allergy Clin Immunol. 1996;97:1413-4.

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Urticaria–Angioedema Due to Limpet Ingestion

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Key words: Limpet. *Patella vulgata*. Urticaria. *Dermatophagoides pteronyssinus*. Cross-reactivity.

Palabras clave: Lapa. *Patella vulgata*. Urticaria. *Dermatophagoides pteronyssinus*. Reactividad cruzada.

A 16-year-old male presented with urticaria and facial angioedema affecting the lips, tongue, and both eyelids 30 to 45 minutes following the ingestion of limpet. There was no associated asthmatic symptomatology. Emergency treatment with antihistamines and parenteral corticosteroids was required to resolve the condition. The patient had not experienced previous adverse reactions following the ingestion of, or contact with, this shellfish, and he also tolerated the ingestion of crustaceans (prawns) and other seafood, including bivalve molluscs (clams, mussels, cockles), cephalopods (octopus, cuttlefish, squid), and tuna.

The patient also described irritation of the eyes and nose in the spring months, with no associated dry cough or wheezing; these symptoms did not appear during the remaining months

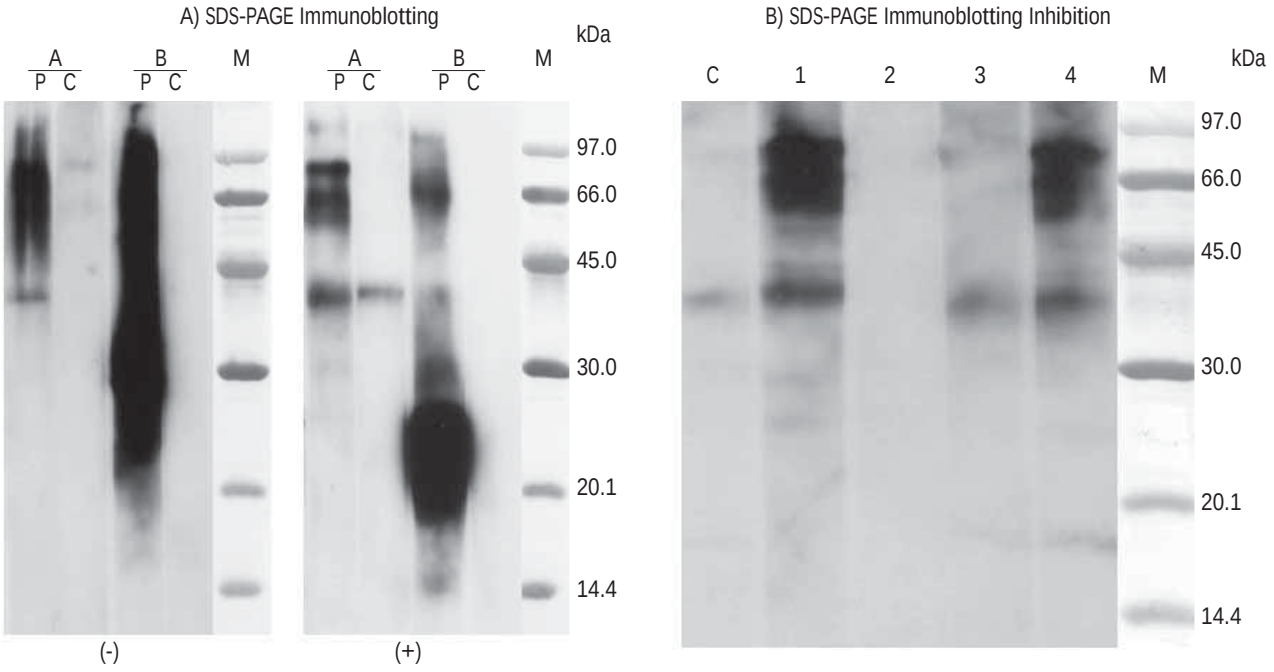

Figure. A, SDS-PAGE immunoblotting. A corresponds to the cooked limpet extract and B to the *Dermatophagoides pteronyssinus* extract. Lane P, patient serum; lane C, control serum (pooled sera from nonatopic patients); lane M, molecular mass marker; (-), samples without 2-mercaptoethanol treatment, (+) samples with 2-mercaptoethanol treatment. B, SDS-PAGE immunoblotting inhibition. Limpet extract was used as the solid phase. Lane C, control serum; lane 1, patient serum; lane 2, patient serum preincubated with limpet extract; lane 3, patient serum preincubated with *D pteronyssinus* extract; lane 4, patient serum preincubated with lamb extract; lane M, molecular mass marker. SDS-PAGE indicates sodium dodecyl sulfate polyacrylamide gel electrophoresis.

of the year. He was in contact with dogs and birds in the home environment.

Skin prick tests (SPTs) to common aeroallergens were positive for *Dermatophagoides pteronyssinus* (wheal diameter, 11 mm), *Dermatophagoides farinae* (9 mm), *Tyrophagus putrescentiae* (7 mm), *Lepidoglyphus destructor* (6 mm), *Blomia kulagini* (3.5 mm), *Cladosporium herbarum* (3 mm), dog epithelium (3 mm), cat epithelium (3 mm), grass pollen (3 mm), and latex (3-4 mm). Prick to prick testing with uncooked limpet was also positive (3-4 mm), as was a skin rub test (erythema, 4 mm; wheal, 3 mm). SPTs were positive for uncooked and cooked limpet extract (Bial-Aristegui, Bilbao, Spain) (3 mm and 3.5 mm, respectively), doubtful for mussel extract (Bial-Aristegui) (2-3 mm), and negative for prawn, octopus, and cuttlefish extracts and *Anisakis simplex* (Bial-Aristegui). A negative SPT response to limpet extract was observed in 5 subjects sensitized to *D pteronyssinus* who served as the control group.

As far as in vitro testing was concerned, total immunoglobulin (Ig) E was 253 IU/mL and positive allergen-specific IgE was 94.6 kU/L for *D pteronyssinus*, 15.1 kU/L for *D farinae*, and 0.50 kU/L for mixed grass pollen. Tests were negative (<0.35 kU/L) for olive pollen, anchovy, tuna, *A simplex*, cuttlefish, mussel, prawn, king prawn, barnacle, and octopus. Specific IgE for uncooked and cooked limpet measured by enzyme allergosorbent test (Hytec, Hycor Biomedical Ltd, Penicuik, UK) was 0.4 kU/L and 0.9 kU/L, respectively.

Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) immunoblotting revealed IgE-binding proteins of 81 kDa, 64 kDa, and 58 kDa in the limpet extract (Figure). IgE binding was completely inhibited by *D pteronyssinus* in SDS-PAGE immunoblotting inhibition (Figure).

The limpet (*Patella vulgata*) is a mollusc belonging to the Gastropoda class, order Archaesgastropoda [1]. Although IgE-mediated food allergies are common, few cases citing limpet as the causative agent have been reported, probably due to its limited consumption [1-9].

In this paper we have reported the involvement of an IgE-mediated mechanism in an immediate reaction following the ingestion of limpet. Unlike the majority of the cases reported in the literature, in which severe asthma exacerbation is the most frequent immediate clinical response to limpet ingestion, we describe a case of IgE-mediated urticaria and angioedema [1-4,7,9], confirmed by skin tests and specific IgE determinations.

It is worth noting that our patient was sensitized to the house dust mite *D pteronyssinus*, as were the majority of patients reported in the literature consulted [1,2,4,6,8,9]. This prompted us to investigate the existence of cross-reactivity between limpet and *D pteronyssinus*.

The immunoblotting inhibition assay showed that the *D pteronyssinus* extract produced complete inhibition of IgE-binding in the limpet extract (bands of 81 kDa, 64 kDa, and 58 kDa), thus revealing the existence of cross-reactivity between the 2 allergenic sources (Figure). Consequently,

the house dust mite allergy presented by this patient may have predisposed him to allergic symptoms following limpet ingestion.

References

1. Azofra J, Lombardero M. Limpet anaphylaxis: cross-reactivity between limpet and house-dust mite Dermatophagoides Pteronyssinus. Allergy. 2003:58(2):146-9.
2. Thong BYH, Cheng YK, Leong KP, Tang CY, Chng HH. Immediate food hypersensitivity among adults attending a clinical immunology/allergy centre in Singapore. Singapore Med J. 2007 Mar; 48(3):236-40.
3. Morikawa A, Kato M, Tokuyama K, Kurome T, Minoshima M, Iwata S. Anaphylaxis to grand keyhole limpet (abalone-like shellfish) and abalone. Ann Allergy. 1990;65:415-7.
4. Carrillo T, Rodríguez de Castro F, Blanco C, Castillo R, Quiralte J, Cuevas M. Anaphylaxis due to limpet ingestion. Ann Allergy. 1994;73(6):504-8.
5. García JC, Bartolomé B, De La Torre F, Martínez A, Martínez J. Sensibilización a lapa (Patella spp.) en pacientes con reacciones de hipersensibilidad al marisco. Rev Esp Alergol Inmunol. 1996;11(2):147-8.
6. Rodríguez V, Baeza ML, Ordagui E, Zubeldia JM, Rodríguez JJ, González MC, Luna I, Marcos C, González R. Prevalencia de sensibilización a crustáceos en una población sensible a ácaros. Rev Esp Alergol. 1996;11(2):148.
7. Joral A, Navarro JA, Villas F, Garmendia J, Villareal O. Limpet anaphylaxis. Allergy. 1997;52(37):117.
8. Taylor SL. Molluscan Shellfish allergy. Adv Food Nutr Res. 2008;54:139-77.
9. Carrillo T, De Castro FR, Cuevas M, Caminero J, Cabrero P. Allergy to Limpet. Allergy. 1991;46:515-9.

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