Fixed Drug Eruption Due to Nabumetone in a Patient With Previous Fixed Drug Eruptions Due to Naproxen

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Key words: Cross-reactions. Fixed drug eruption. Nabumetone. Naproxen. Nonsteroidal anti-inflammatory drugs.

Palabras clave: Reacciones cruzadas. Exantema fijo medicamentoso. Nabumetona. Naproxeno. Antiinflamatorios no esteroideos

Nabumetone is a nonacidic nonsteroidal anti-inflammatory drug (NSAID) formulated as a pharmacologically inactive prodrug that becomes active only after absorption, predominantly in the small intestine, and through hepatic conversion to its active metabolite, 6-methoxy-2-naphthylacetic acid (6-MNA). This metabolite is structurally similar to naproxen, and is a potent inhibitor of prostaglandin synthesis, preferentially via the cyclooxygenase-2 (COX-2) pathway [1]. Nabumetone has been recommended as a safe alternative in most patients with hypersensitivity reactions to NSAIDs [2].

A 52-year-old woman complained of various episodes of itching, burning, and erythematous plaques—one on her forehead (1-2 cm diameter) and the other in the infraclavicular area (5 cm diameter)—in the previous 2 years. The plaques became red-brown and disappeared within 1 week without treatment. With time, the infraclavicular lesion persisted as brown pigmentation. After various episodes the patient noticed that the eruption might be related to the intake of naproxen tablets, but she was not sure. The last episode had occurred 1 year before consultation and she had subsequently tolerated oral acetylsalicylic acid, paracetamol, and ibuprofen.

In order to confirm the suspicion of fixed drug eruption (FDE) due to naproxen, patch tests (30% in petrolatum) were carried out with this drug and other propionic acid derivatives (ibuprofen, dexibuprofen, ketoprofen, dexketoprofen, flurbiprofen, and ketorolac) and NSAIDs (diclofenac, indomethacin, benzydamine, bufexamac, phenylbutazone, piroxicam, and nabumetone). The tests were performed on previous lesions with naproxen and on the back (normal skin) with all the drugs mentioned. Readings at 48 and 96 hours were negative in all cases. An oral challenge test with naproxen was performed in the hospital after obtaining informed consent. Two hours later, lesions with the same characteristics as those described earlier reappeared at the same locations. With the purpose of identifying safe alternatives to naproxen, we performed oral challenge tests with dexketoprofen and nabumetone 6 weeks later. While dexketoprofen proved negative, nabumetone (1 g) produced an identical reaction to that induced by naproxen 2 hours after administration. The patient had not taken nabumetone previously.

Nabumetone is generally a well-tolerated NSAID. The most frequent adverse effects are those commonly seen with COX inhibitors, namely diarrhea, dyspepsia, headache, abdominal pain, and nausea. Dermatological reactions such as pseudoporphyria have been associated with nabumetone, but systemic hypersensitivity reactions are not common [1]. To our knowledge, this is the first report of FDE due to nabumetone and our case is particularly interesting because our patient had experienced previous FDE to naproxen. NSAIDs are common offending agents in FDE, and FDE to naproxen has been reported in single case reports and in some studies with a prevalence ranging from 3% [3] to 23% [4]. Lesions induced by naproxen frequently affect the lips, the face, and the neck [4]. False negative results are common when testing topical naproxen on both normal skin and previous FDE lesions, and oral provocation is still the most reliable method for the diagnosis of FDE [5,6]. Although cross-reactivity between drugs with similar molecular structures is possible, in a previous study, we did not find cross-reactivity between naproxen and other propionic acid derivatives [6]. However, in the case reported here, the administration of nabumetone (a naphthylalkanone NSAID) was positive. In our opinion, the similarity of the chemical structure of naproxen and the active metabolite of nabumetone could be the reason for this reaction. Because there are no references in the literature to nabumetone intolerance in patients with FDE to naproxen, we believe that our case is interesting as it might help to prevent such reactions in the future.

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Hand Contact Dermatitis Made a Patient Blind for the Second Time!

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Key words: Exotic wood, wood contact dermatitis. *Quercus robur*, *Fagus sylvatica*. *Gossweilerodendron balsamiferum*.

Palabras clave: Madera exótica. Dermatitis de contacto por madera. *Quercus robur. Fagus sylvatica. Gossweilerodendron balsamiferum*.

Wood contact dermatitis is a rare condition, but it is frequently reported in occupational contexts, especially in association with tropical woods [1]. Sensitization in such cases is related to direct or airborne exposure to wood dust [1]. There have been only rare reports of sensitization to solid wood and finished wood products such as instruments, wooden jewelry, and knife handles [1].

We report the case of a 38-year-old woman, blind since the age of 15 years due to retinal detachment, who developed contact dermatitis after exposure to wood. In the previous 14 months, she had developed erythema on both hands, as well as severe lesions consisting of erythematous lichenified plaques alternating with vesicles, particularly affecting the tips of the fingers. The lesions resulted in dreadful itching and a progressive loss of sensitivity that prevented the patient from reading Braille. No other lesions were observed at any other skin sites. Symptoms were only partly controlled with local and systemic corticosteroid treatment, with incomplete remission of skin lesions. Allergic persistent moderate/severe rhinitis to *Dermatophagoides pteronyssinus* had been previously diagnosed. The patient underwent patch testing with the European baseline series (Chemotechnique Diagnosis, Vellinge, Sweden). Allergens were applied on the upper back using 8 mm Finn Chambers (Epitest, Oy, Finland). The readings were noted on days 2 and 4 according to International Contact Dermatitis Research Group criteria. All the results were negative.

A careful evaluation of the patient's routine revealed the use of wood in writing equipment (*Jugulans nigra, Fagus sylvatica*), a walking stick (*Swietenia mahogani*), door handles (*Quercus robur, Pinus monticola*), a working desk (*Chlorophora excelsa*) and a piano used daily for teaching (*Swietenia mahogani, Gossweilerodendron balsamiferum*). We performed patch tests with natural dust from these woods (10% in petrolatum). The patches were left in place for 48 hours and readings recorded at 48 hours (1 hour after removal) and 72 hours. The results were positive for *G balsamiferum, F sylvatica*, and Q robur (++, strong reaction for all) at 48 hours, with persistence of lesions at 72 hours. The same tests carried out in 2 healthy individuals and 2 patients with nickel contact dermatitis were negative.

The exhaustive investigation of less common potential contact allergens was essential for the diagnosis of contact dermatitis to wood in our patient, with results showing sensitization to 1 exotic wood (*G balsamiferum*) and 2 nonexotic woods (*F sylvatica and Q robur*) through exposure to finished articles.

Contact dermatitis to exotic wood has been reported in the past [2,3], but we found no recent reports. Sensitization to *F sylvatica*, in contrast, has been rarely reported in the past, but there have been some recent cases described in occupational settings [4,5]. *Q rubor* seems to be less likely to induce contact dermatitis, with only 1 report of 3 patients in the literature [6]. The negative results to allergens from the European baseline series used in the preparation of wood varnishes, resins, and preservatives corroborate exclusive sensitization to wood.

Complete avoidance of the objects made with the woods to which our patient was sensitized resulted in the remission of skin lesions. The specific diagnosis was essential in this particular case as it allowed us to propose specific measures to help the patient, who was blind, to recover her ability to read braille and therefore regain quality of life.

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Urticaria Due to Articaine

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Key words: Amide. Articaine. Local anesthetic. Urticaria.

Palabras clave: Amida. Articaina. Anestésico local. Urticaria.

Local anesthetics are very common drugs. Although usually well tolerated, they can precipitate adverse reactions of different types and severity. These reactions can be directly related to the anesthetic (allergic reaction/idiosyncratic), to the doses administered (toxic reaction or overdosage), or to psychogenic/vasovagal factors (fear and anxiety).

We report the case of a 25 year-old woman with a personal history of rhinoconjunctivitis due to pollen sensitivity, who, 30 minutes after the subcutaneous administration of Ultracain (articaine and epinephrine) for a dental procedure, developed generalized pruritus, facial edema, and hives on the face, neck, and thorax. The symptoms were treated with parenteral antihistamines and corticosteroids. She had previously tolerated Ultracain and had never had urticaria before.

The patient was referred to our allergy department, where she underwent an allergy study after giving her informed consent.

Prick tests with aeroallergens were positive to house dust mites, dog and cat dander, and pollen. A latex prick test was negative. Prick and intradermal tests performed with Ultracain and epinephrine were negative. Subsequently, a graded-dose subcutaneous challenge with Ultracain (articaine without epinephrine was not available) up to 2 mL was performed. Twenty minutes after the administration of a cumulative dosis of 0.6 mL, the patient developed pruritus and urticarial lesions on the neck, trunk, and forehead. She was treated with parenteral antihistamines and corticosteroids and the lesions cleared in an hour.

A cross-reactivity study was performed in order to identify an alternative local anesthetic. Skin prick and intradermal tests with mepivacaine, lidocaine, and bupivacaine were negative, and subcutaneous challenge tests with mepivacaine, lidocaine, epinephrine, and bupivacaine were all well tolerated. Preservatives were ruled out as the etiologic agent because the patient tolerated other drugs containing the same excipient as that used in Ultracain (bisulfite).

The literature shows that immediate allergic reactions to local anesthetics are rare, with a reported prevalence of less than 1% [1-3]. Articaine is one of the most widely used anesthetics in dental procedures but there are few cases published in the literature of allergy to this drug. Warrington and McPhillips [4] reported the case of 35-year-old woman who developed generalized giant hives 5 minutes after an injection of Ultracain. Skin prick and intradermal tests performed with prilocaine and bupivacaine were positive, and a subcutaneous challenge test performed with procaine was also well tolerated.

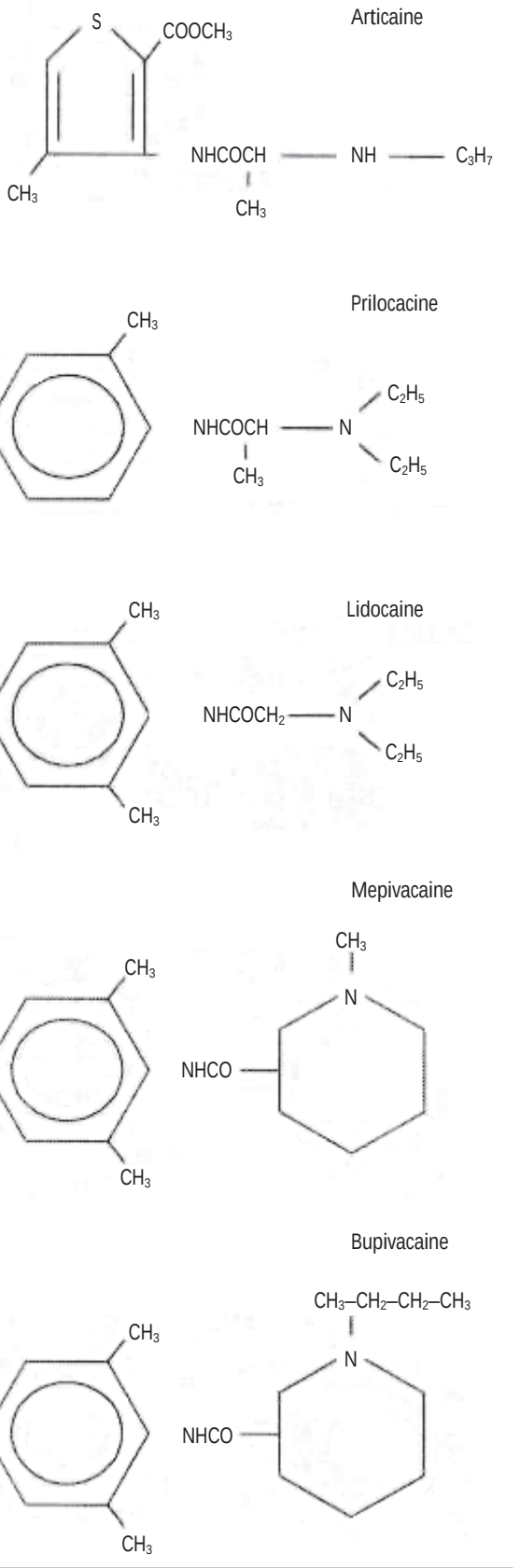

Figure. Local anesthetics from the amide group.

El-Qutob et al [1] described the case of a 51-year-old woman who experienced erythema and facial edema after the administration of Ultracain. Skin prick tests were negative for epinephrine, lidocaine, mepivacaine, and bupivacaine, and positive for articaine. A subsequent subcutaneous challenge test with mepivacaine was negative. On the basis of the allergy study, the authors concluded that there was no cross-reactivity between articaine and the other anesthetics in the amide group. Our patient developed an adverse reaction after a subcutaneous challenge with articaine, but the cross-reactivity study showed tolerance of the other local anesthetics in the amide group, as reported by El-Qutob et al. One possible explanation is that although articaine is an amide, it has a substitute thiophene ring instead of a methylated phenyl ring (Figure) [5]. We believe that our patient is sensitized to this thiophene ring. The difference in the ring of the chemical structure may explain the lack of cross-reactivity between articaine and other amide local anesthetics [1,3].

In conclusion, although skin prick and intradermal tests were negative in our patient, her history and the positive subcutaneous challenge test strongly suggest that she did experience an immediate sensitivity reaction to articaine. We have demonstrated the lack of cross-reactivity with lidocaine, mepivacaine, and bupivacaine by challenge testing. To the best of our knowledge this case is one of the few cases of articaine allergy that has been reported in the literature.

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Global Research Productivity in Allergy

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Key words: Allergology. Bibliometric analysis. Impact factor. Medical journals. Worldwide trends in research.

Palabras clave: Alergología. Análisis bibliométrico. Factor de impacto. Revistas médicas. Tendencias mundiales de investigación.

The term allergy is used to describe a variety of human disorders that manifest as symptomatic responses of the immune system to otherwise harmless environmental triggers [1,2]. The prevalence of allergic disorders has increased considerably over the last few decades, generating a considerable economic burden for society [3-5] and leading to increased production of related research, which aims to provide better screening methods and improved therapeutic modalities. The goal of the present study was to assess the quantitative and qualitative contribution of different geographical regions to research activity in the field of allergy.

We used a methodology similar to that of other authors [6,7] and were able to identify 23 journals listed in the Allergy category of the 2009 Science Citation Index Expanded-Journal Citation Reports database [8]. We finally included 15 journals that were also listed in the PubMed database [9] and had an impact factor. A total of 28 050 articles produced during the period 1995-2008 were retrieved; 99.74% of these contained sufficient data to classify them according to their place of origin (Table).

Our results show that Western Europe and the USA are the leading regions in terms of quantity (total production of articles); however, other regions, such as Canada and Oceania, are the leaders in terms of quality. When we consider the population and annual gross domestic product of each region, both Canada and Oceania improve their rank considerably; this is a direct effect of the high quality of articles produced in these regions. The developing countries of Eastern Europe, Latin America and the Caribbean, Asia (excluding Japan), and Africa generally account for a small portion of research productivity.

Interestingly, in all categories, Western Europe is the leading region in the field of allergy. Closer consideration of the contribution of individual countries in Western Europe reveals that, in terms of the total number of articles produced, the United Kingdom, Italy, and Germany rank in the first 3 places. When we take into account economic criteria, the leading countries are Finland, Sweden, and Denmark.

Our results demonstrate that developed countries, which invest more money in biomedical research, have a high quantity and quality of research production.

Although it provides a representative illustration of general trends in global allergy research, our study has certain

Table. Global Research Productivity Indexes in the Field of Allergy During the Period 1995-2008

World area	Total Number of Articles	Mean Impact Factor[a]	Total Product[b]	Total Product According to Population	Total Product According to GDP
Western Europe	13 602	4.53	61 440	35.4	11.5
Iceland	12	5.90	71	38.0	17.6
Ireland	47	3.85	181	7.9	3.3
United Kingdom	2301	4.54	10 506	36.6	12.5
Spain	1727	4.12	7121	50.5	12.7
Portugal	139	3.69	513	22.1	3.5
France	987	4.78	4714	16.7	5.4
Netherlands	859	4.74	4071	50.6	18.1
Belgium	374	4.61	1724	32.6	11.5
Switzerland	487	4.92	2395	48.8	23.2
Germany	1794	4.65	8351	21.9	7.3
Italy	1948	4.38	8530	36.0	10.5
Denmark	602	4.39	2646	77.0	35.2
Austria	512	4.70	2406	59.6	21.1
Norway	172	4.95	852	21.7	13.5
Finland	608	4.75	2890	115.8	39.8
Sweden	1033	4.59	4744	103.2	37.8
USA	7336	4.63	33 989	21.4	8.4
Canada	818	5.87	4804	32.0	10.9
Japan	2031	3.92	7961	14.0	4.5
Oceania	769	4.76	3664	33.5	6.1
Asia (excluding Japan)	1910	3.15	6009	7.7	0.1
Eastern Europe	990	3.18	3149	10.6	0.5
Latin America and the Caribbean	481	3.17	1525	4.3	0.2
Africa	113	4.01	453	3.5	0.0

Abbreviation: GDP, gross domestic product.
[a]The mean impact factor is an index of quality.
[b]The total product of articles is an integrated index of quantity and quality (number of articles × impact factor).

limitations. First, the PubMed search engine did not include all the journals listed in the Journal Citation Reports database, with the result that we had to exclude 2 journals that did not have an impact factor. This raises another controversial issue, namely, whether impact factor is a credible and useful means of indexing quality, even though no other generally acceptable alternative has been proposed [10]. Furthermore, we cannot exclude the presence of journals not listed in the Institute for Scientific Information database and local journals, which also contribute to total research production. Finally, as PubMed provides only the address of the first author, we were unable to take account of the many articles that are the result of multinational cooperation.

In summary, the present study is the first attempt to analyze worldwide trends in research productivity in the field of allergy for the period 1995-2008. Western Europe is the leading region. Other developed countries, such as the USA, Canada, and Oceania rank high, especially if we take into account economic criteria. Developing countries, on the other hand, provide only a small contribution to research productivity.

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The Basophil Activation Test as a Promising Diagnostic Tool in Hypersensitivity to Chironomid Larvae

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Key words: Anaphylaxis. Basophil activation test. *Chironomus*. Diagnosis. Fish food.

Palabras clave: Anafilaxia. Test de activación de basófilos. *Chironomus*. Diagnóstico. Comida para peces.

Chironomids are nonstinging insects belonging to the Nematocera suborder of the Diptera order. They are found in wetlands and are a frequent cause of environmental allergy in Sudan, Japan, Egypt, and the northern part of the United States [1]. However, in recent years, hypersensitivity to chironomids has been reported after occupational exposure in fish food handlers (fish food factories, fishermen, pet shops.) [2] and in relation to hobbies in countries where *Chironomus* larvae (*Chironomus thummi*) are commercialized as fish food [3]. Hypersensitivity to these larvae has been reported to cause urticaria, rhinoconjunctivitis, asthma, angioedema, and even anaphylaxis [3,4].

Conventional diagnosis is made using the skin prick test with chironomid extract and specific immunoglobulin (Ig) E against *C thummi*. However, the allergenic potential of *Chironomus* larvae carries a risk when the noncommercial extract is used in skin tests, and cases of anaphylaxis have been reported when these tests were performed [4].

We report the case of a 33-year-old woman with an unremarkable clinical history. Immediately after feeding her fish with *Chironomus* larvae (Tetra Delica, Tetra, Spectrum Brands, USA) 10 days previously, the patient suffered from bouts of sneezing, itching in the nose and eyes, rhinorrhea, and epiphora followed a few minutes later by ocular angioedema and dizziness. This clinical picture persisted with difficulty in breathing, wheezing, and dry cough for which she took terbutaline. Her symptoms improved slowly, although the rhinorrhea and nasal obstruction persisted. She had previously handled the same fish food with no problems. However, on the day of the reaction, she had rubbed the dry *Chironomus* larvae between her fingers to break them into smaller pieces before dropping them into the fish tank.

Two weeks after her first consultation and with all her symptoms having resolved, a skin prick test was performed with a battery of common inhalant and food allergens including pollens, dust mite, fish, shellfish, *Anisakis*, cockroach, and common mosquito (*Aedes communis*), all of which were negative. We performed a further skin prick test with an extract of freeze-dried *Chironomus* larvae (Tetra Delica 20% w/v in phosphate-buffered saline), which was positive (29 × 13 mm), and determined specific IgE to C thummi (41.70 kU_A/L). Five skin prick tests were performed with *Chironomus* in control patients and the results were negative. A few minutes after the skin test, the patient began to report a sensation of nasal obstruction and pharyngeal foreign body, but not breathing difficulties. Examination revealed no apparent edema of the uvula. She was administered 5 mg of levocetirizine and her clinical picture gradually resolved. A basophil activation test using CD63 as a marker for activated basophils (FACSCanto, BD Biosciences, San José, California, USA) was performed with *C thummi* extract (6 mg/mL) with a positive result at all the concentrations tested (29.8% at 3 mg/mL, 25.5% at 0.3 mg/mL, 20.6% at 0.03 mg/mL, 20.5% at 3 μg/mL; baseline activation, 2.3%; anti-IgE, 42.1%) (Figure). The test was carried out in parallel in 4 controls and the results were negative.

We present a case of allergy to *C thummi*, with positive results in the skin prick test, specific IgE determination, and basophil activation test. To our knowledge, this is the first report of an allergy to *Chironomus* in which the basophil activation test [5] was performed as part of the allergy workup. Given the risk not only of serious local reactions [6], but also of severe systemic reactions [4] when a prick-prick test with *Chironomus* is used, we believe that the basophil activation test is a highly useful tool in the diagnosis of allergy to *C thummi*.

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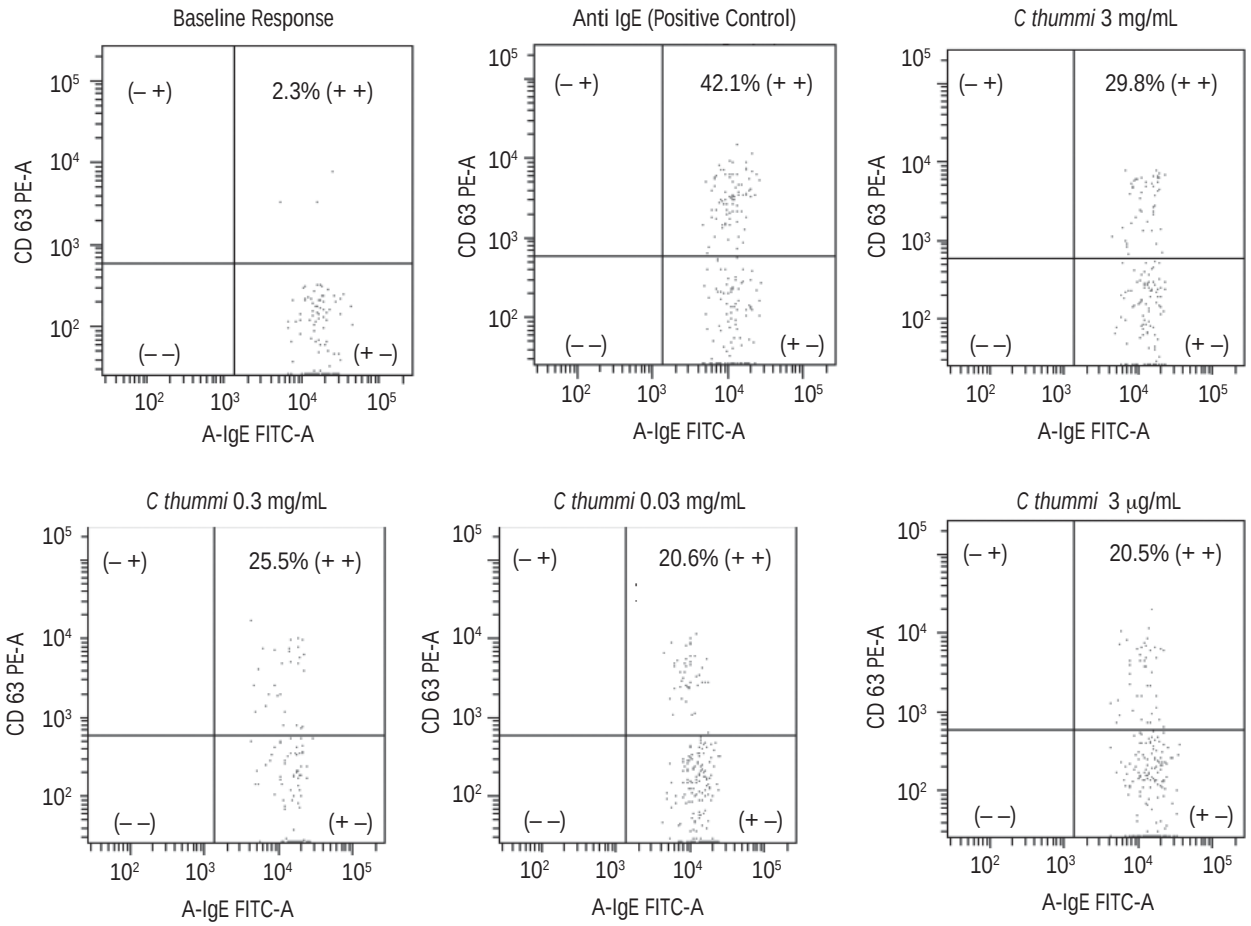

Figure. Basophil activation test with *Chironomus thummi* extract (6 mg/mL). Results of the different concentrations tested.

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Olive pollen (*Olea europaea*) is considered to be one of the main causes of allergic respiratory disease in Mediterranean countries [1]. However, despite the high prevalence of allergy to olive pollen presenting as seasonal rhinoconjunctivitis or asthma and the high consumption of olive fruit, only 2 cases of olive fruit allergy have been reported [2,3].

We present the case of a 16-year-old boy with a history of seasonal rhinoconjunctivitis and asthma that had been successfully treated over a 5-year period with subcutaneous immunotherapy (SCIT) based on a pollen extract vaccine (40% *O europaea* pollen, 30% *Lolium perenne* pollen, 30% *Salsola kali* pollen) at 1500 UBE/mL. He developed pruritic wheals on the arms and upper part of the thorax associated with oppressive retrosternal pain and moderate dyspnea 20 minutes after eating olives. Skin prick testing (SPT) performed with commercial extracts was positive to the following pollens: *L perenne* (6×7 mm), *O europaea* (8×8 mm), *Cupressus arizonica* (4×5 mm), *Artemisia vulgaris* (3×4 mm), and *S kali* (5×6 mm). SPT with profilin and lipid transfer protein (ALK-Abelló, Madrid, Spain) was positive (5×5 mm). The prick-by-prick test to olive fruit was also positive (5×7 mm). SPT was negative in 5 control patients.

Specific immunoglobulin (Ig) E concentrations (CAP-FEIA, Phadia, Uppsala, Sweden) were 42.5 kU_A/L for *L perenne* pollen, 6.46 kU_A/L for *A vulgaris* pollen, 1.04 kU_A/L for *C arizonica* pollen, 0.76 kU_A/L for *S kali* pollen, 0.51 kU_A/L for *O europaea* pollen, and <0.35 kU_A/L for profilin. Likewise, specific IgE determined using the enzyme allergosorbent test (HYTEC, HYCOR Biomedical Ltd, UK) was positive for olive fruit (1.0 kU_A/L), olive seed (1.6 kU_A/L), and peach LTP (Pru p 3, 3.2 kU_A/L). An immunoblot-inhibition study (Figure) with olive fruit extract in the solid phase showed almost complete inhibition with olive pollen extract, less intense inhibition with grass pollen extract, and partial inhibition with extracts from Russian thistle pollen and olive fruit. An oral challenge test with olive fruit induced urticaria and mild bronchospasm 20 minutes after eating 7 units.

SPT, specific IgE, and a challenge test with olive fruit confirmed the food allergy. The original aspect of this case is

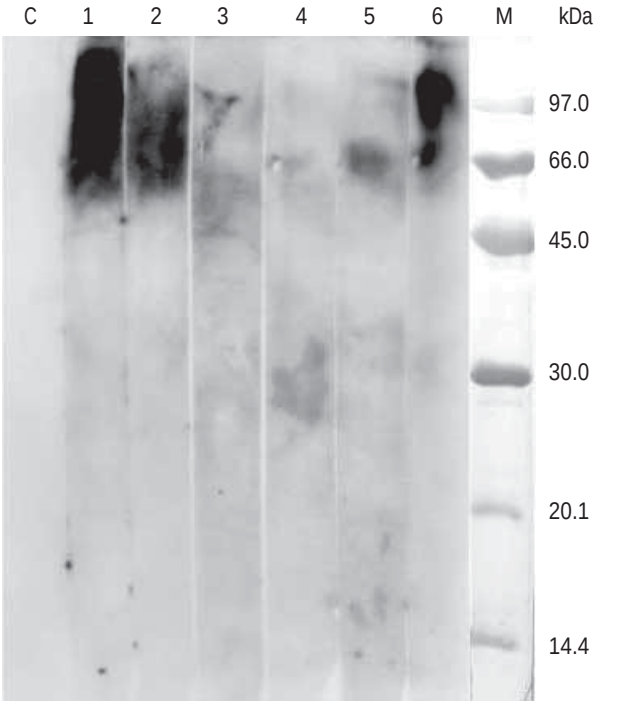

Figure. Immunoblot-inhibition study.
Lane C, Control serum (mixture of sera from nonatopic individuals). Lane 1, Patient's serum. Lane 2, Patient's serum pre-incubated with olive fruit extract (0.8 mg/mL) (homologous inhibition with positive control of inhibition). Lane 3, Patient's serum pre-incubated with *Lolium perenne* pollen extract (0.8 mg/mL; 60 μg/mL Lol p 1; 30 μg/mL Lol p 5). Lane 4, Patient's serum pre-incubated with *Olea europaea* pollen extract (0.8 mg/mL; 100 μg/mL Ole e 1). Lane 5, Patient's serum pre-incubated with *Salsola kali* pollen extract (0.8 mg/mL; 30 μg/mL Sal k 1). Lane 6, Patient's serum pre-incubated with extract of raw lamb (0.8 mg/mL). M, Pattern of molecular masses.

that the urticarial lesions developed only in the areas in which the aluminium-adsorbed SCIT had been administered. This type of SCIT slowly releases allergens that can persist for several months in the area of administration, causing a foreign-body reaction to aluminium hydroxide and an immunological interaction with the administered antigen [4]. The location of the lesions at the previous sites of SCIT suggests activation of immunological memory after exposure to a different antigen (olive fruit) that has common allergenic structures with the pollens. Maximum inhibition of blotting was observed with the *O europaea* pollen extract.

In contrast to the case reported by Azofra [2], our patient was also allergic to pollens; therefore, sensitization to olive fruit could therefore be due to cross-reactivity between the pollen and the fruit of the same tree, as has been reported for grape and vine pollen [5] and for hazelnut and hazel pollen [6]. Ünsell et al [3] described a patient in whom primary sensitization to *O europaea* pollen occurred 3 years before developing allergy to olive fruit. However, in our case, we extended the study with an immunoblot-inhibition test, which

showed the IgE binding bands responsible for the tree-pollen cross-reactivity, and we performed an oral challenge test with the implicated fruit.

Hyposensitized patients develop persistent subcutaneous nodules at the injection site in 0.5%-6% of cases. These nodules are usually painful and pruritic and may last for several years. In our region, *O europaea* allergy is very common (60% of patients attending the clinic), as is eating olive fruit. Consequently, we are surprised not to have detected more cases. We believe that this phenomenon could occur with SCIT for other pollens and their corresponding fruits and that it could provide the basis for several publications.

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