Acute Abdomen in a Patient With Homozygous Type I Hereditary Angioedema: Rapid Improvement in Computed Tomography Scans After C1 Inhibitor Replacement

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Hereditary angioedema (HAE) due to C1-inhibitor deficiency is a rare autosomal dominant disease characterized by recurrent episodes of transient localized swelling of the subcutaneous and/or mucosal tissues that can occur anywhere in the body. Acute abdominal pain due to mucosal swelling of the gut is one of the most common presentations of HAE, leading frequently to unnecessary abdominal surgery such as exploratory laparotomy and appendectomy.

We report the case of a patient with a previous diagnosis of HAE who experienced an episode of severe acute abdominal pain with striking computed tomography (CT) findings that resolved rapidly after intravenous infusion of a C1 esterase inhibitor (C1-INH) concentrate and no other therapy. The patient had type I HAE in homozygosis, ie, a mutation affecting the coding region of *C1INH* in both alleles, which is extremely rare. His only treatment was low-molecular-weight heparin injections for acute angioedema attacks.

The patient was a 22-year-old man who presented at the emergency department with diffuse abdominal pain that had begun the previous day. He had no other gastrointestinal or general symptoms. He had a history of HAE with a specific familial homozygous mutation in the *C1INH* gene, which was the subject a previous publication by our group [1] and a detailed editorial comment [2]. The patient was allergic to nuts and rosaceae and smoked 10 cigarettes a day. Initially, he received therapy with stanozolol (2-4 mg/d) for several months, although this was withdrawn because of undesirable androgenic effects (including alopecia) and a poor response with frequent angioedema attacks. Two years ago, he experienced an episode of deep thrombosis and pulmonary embolism of unknown cause that resolved after fibrinolysis and treatment with subcutaneous dalteparin (150 mg). The presence of antiphospholipid antibodies and hypercoagulability-associated conditions other than smoking was ruled out. Angioedema of the lip, eyelid, and limbs resolved immediately; therefore, the patient continued self-treating acute angioedema attacks with dalteparin, but took no prophylactic treatment. The clinical response was good, and no bleeding complications were recorded. The patient was lost to follow-up.

In July 2012, the patient presented at our emergency department with colicky abdominal pain in the right hypochondrium and intermittent nausea that had begun 12 hours earlier. The pain was not accompanied by skin lesions, fever, or other gastrointestinal or general symptoms. He denied having taken drugs or suspicious foods during the previous days. The physical examination was unremarkable, with an axillary temperature of 36.7ºC, blood pressure of 141/55 mmHg, and pulse rate of 83 bpm. The abdomen was flat, tender, nondistended, with slight pain on palpation. Bowel sounds were present. Percussion was negative. An abdominal

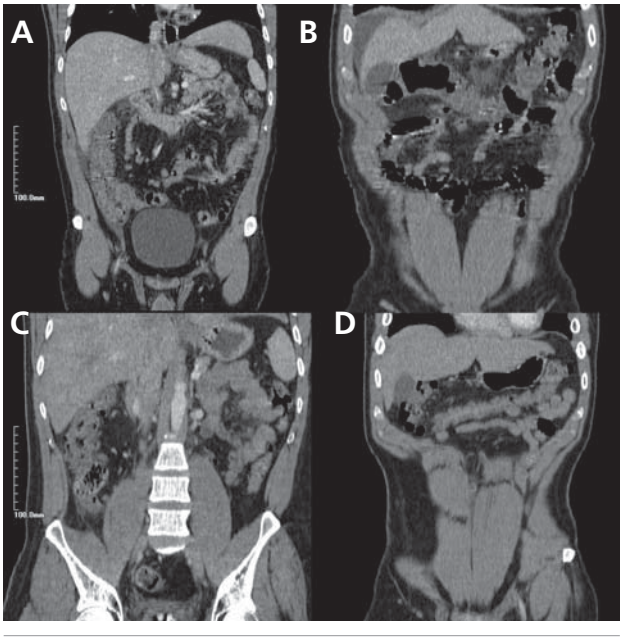

Figure. Abdominopelvic computed tomography scan before and after intravenous infusion of C1-INH. Coronal reconstruction. A, Diffuse hypodense thickening of the ascending colon and ileocecal region before therapy. B, Thickening of the transverse colon before therapy. C and D, Marked reduction in inflammatory swelling of the transverse colon, ascending colon, and cecum 12 hours after intravenous infusion of C1-INH.

plain radiograph showed stool and gas in the colon. Laboratory tests revealed mild leukocytosis with left shift; the results of the blood and biochemistry analyses, including liver function, amylase, and urinalysis, were normal. A CT scan of the abdomen revealed thickening of the cecal wall and transverse colon wall, as well as free intraperitoneal fluid, mainly in the right flank. A small, nonspecific enlarged mesenteric lymph node (<1 cm) was observed (Figure, A and B).

The abdominal pain improved spontaneously within a few hours in the emergency department. However, taking into account the patient's antecedents and his striking CT findings, complement analysis was performed (including C4, C2, C1q, and C1-INH levels) and provisional treatment with pasteurized concentrate of C1-INH (Berinert, CLS Behring) was prescribed. Two vials (total 1000 U) were administered intravenously and the patient remained under observation in the emergency department for the next 12 hours. A second control CT scan of the abdomen with intravenous iodinated contrast revealed a marked reduction in the inflammatory edematous component of the colonic wall and absence of mesenteric fluid. Minimal lymphadenopathy persisted (Figure, C and D). The patient was finally discharged with no symptoms. The results of the physical examination were normal, and he was referred to our allergy outpatient department for follow-up.

HAE is a rare primary immunodeficiency affecting about 1:10 000 to 1:150 000 people throughout the world [3]. It is the most common genetic defect of the complement system, with 2 main variants: deficiency of functionally active C1-INH (type 1 HAE) and, more rarely, normal levels of dysfunctional C1-INH (type 2 HAE). HAE is an autosomal dominant disorder, and patients are heterozygous, except in specific cases of patients with consanguineous parents 4], as was the case for our patient, who is homozygous for a mutation affecting the coding region of *C1INH* [1].

Severe acute abdominal pain is one of the most common presentations of HAE. Over 90% of all HAE patients experience abdominal pain during acute episodes, and abdominal attacks are almost as common as cutaneous attacks [5], leading frequently to unnecessary abdominal surgery.

Attenuated androgens (danazol or stanozolol) are the most effective and widely used drugs for prophylaxis of HAE, and although their mechanism of action is not known, they are assumed to act by increasing transcription levels of the wild-type allele in the *C1INH* gene [6]. Since homozygous patients lack a wild-type allele, long-term prophylactic treatment with attenuated androgens is not considered useful. Such was the case of the patient we report, who had been taking stanozolol (2-4 mg/d) for several months, with a poor response and frequent angioedema attacks. On the other hand, given the patient's history of thrombosis, prophylaxis with antifibrinolytic agents was not considered appropriate. Therefore, given the initial infrequency of his angioedema attacks, he was encouraged to use intravenous C1-INH concentrate on demand. However, after his previous thrombotic episode, he noted an immediate improvement in the episodes of cutaneous angioedema after treatment with subcutaneous dalteparin: therefore, he continued to take this drug for acute attacks and stopped taking prophylaxis. The patient was subsequently lost to follow-up.

Heparin is a natural proteoglycan produced by mast cells and basophils. It is capable of binding to antithrombin III, although it has other known biologic activities, such as the ability to regulate multiple steps in the complement cascade by acting on both the classical pathway and the alternative pathway [7]. The first suggestions that heparin might be used to treat HAE—albeit on an empiric basis—were made in the 1970s [8]. It was subsequently demonstrated that heparin boosts plasma C1-INH activity 15 to 35-fold in vitro [7]. Prior to the marketing of C1-INH nanofiltrate in the USA, attempts were made to treat HAE with prophylactic inhaled or injected heparin, although the results were discordant [7, 9]. Nadroparin was recently used for the short-term prophylaxis and treatment of angioedema attacks in 29 adults and 5 children with HAE, with reported success rates of around 90% [10].

During the 7 years the patient was self-treating his acute angioedema attacks with subcutaneous dalteparin (150-mg injection, 2-6 injections per year), the response to treatment was good, and bleeding complications were not reported.

In the episode we describe, the patient did not think acute abdominal pain was related to his HAE and therefore did not self-treat. Abdominal pain was associated with leukocytosis, neutrophilia, and abnormal CT findings (colon wall thickening and free intraperitoneal fluid), which resolved almost completely after intravenous administration of C1-INH and no other therapy (Figure).

Patients who are homozygous for the *C1INH* gene might be at increased risk of hypersensitivity reactions to human plasma-derived C1 inhibitor concentrate. However, this was not the case in the present report, as the patient tolerated C1-INH concentrate with no adverse events. Determination of C1-INH antibodies is planned.

After this episode, the patient was encouraged not to continue to use dalteparin injections but to self-treat with either intravenous C1-INH or subcutaneous icatibant (a bradykinin B2 receptor antagonist) for acute attacks. He has received appropriate training to enable him to recognize early symptoms and self-administer the drugs. Nevertheless, the patient refused self-administration of intravenous C1-INH as prophylactic treatment. He is currently trying prophylaxis with stanozolol (2 mg/d), with limited results. Other regimens for prophylaxis, including subcutaneous nadroparin [10], are being considered.

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Conflicts of Interest

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Changes in the Prevalence of Asthma and Chronic Rhinitis in Valencia, Spain: The ORBA Project 1983-2003

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The prevalence of asthma and chronic rhinitis has increased in recent years in most Western countries [1]. This increase varies widely with the country and geographical area analyzed. Comparison is affected by methodological differences.

The approaches used for comparison can be divided into 2 types: a common methodology applied in numerous countries to facilitate comparison, the best example being the International Study of Asthma and Allergy in Children (ISAAC) [2]; and a simple and sensitive procedure in specific geographic areas [3,4] that facilitates monitoring of these areas with replicated studies.

In 2003, we replicated the 1983 and 1993 editions of the ORBA Project in the same areas and schools. Our primary objective was to detect trends in the cumulative prevalence of clinical asthma and chronic rhinitis in children aged 6 to 14 years. The secondary objective was to study the population aged more than 14 years in the same areas (referred to herein as the adult population).

The methodology and the comprehensive questionnaire were identical to those used in the 2 prior editions [3,4]. Data were requested on present or past self-perceived symptoms compatible with bronchial asthma (wheezing and dyspnea on exertion), chronic rhinitis, and adverse effects of drugs during the preceding year. The doctor's diagnosis was accepted.

Questionnaires were completed jointly by children and their parents and returned 48 hours after distribution in the children's schools. Our questionnaire is similar to that published by the International Union Against Tuberculosis and Lung Disease, which serves as a basis for the European Community Respiratory Health Survey (ECRHS) in individuals aged 20 to 44 years [5].

We selected the same districts and schools as in 1983 and 1993, namely, Vallada-Montesa (VM), the rural and outlying area of Orba-Alfafar (ORB), and the Lycée Français (LF), a school with a high socioeconomic level in the city of Valencia.

The results were expressed as a percentage of the total number of questionnaires returned. A minimum of 85% of questionnaires returned in each school was considered acceptable.

Table. Cumulative Prevalence, Prevalence Rate (PR), and Variation in Prevalence by Year (PV/Y 2003/1983) for Children (6 to 14 Years) and Adults (15 to 63 Years)

	Lycée Français Children/Adults			Orba-Alfafar Children/Adults			Montesa-Vallada Children/Adults		
	2003 (%)	PR	VP/Y	2003 (%)	PR	VP/Y	2003 (%)	PR	VP/Y
Asthma	13.7/8.5	1.5/1.4	+0.23/+0.13	9.40/9.6	1.2/2.4	+0.08/+0.28	11.70/5.7	2.1/2.7	+0.31/+0.18
Rhinitis	7.3/12.8	1.0/1.1	+0.005/+0.08	11.3/15.7	4.9/4.2	+0.45/+0.59	8.70/10.2	2.4/5.6	+0.26/+0.42

Changes in prevalence are expressed in 2 ways: first, as the prevalence ratio (PR), which contrasts values recorded in 2003 with those from 1983 and 1993 (PR values higher than 1 indicate an increase in the period under study); second, as the prevalence variation by year (PV/Y), whether positive or negative, following the nomenclature published by Pearce et al [6].

The response rate for the questionnaires exceeded 92% in all the schools. The sample included 696, 342, and 205 children and 1079, 212, and 333 adults corresponding to LF, ORB, and VM, respectively.

Cumulative prevalence increased in all 3 schools, although with varying magnitude.

The results are shown in the Table.

The results of the 2003 edition of the ORBA project are similar to those of the previous ones. Nonhomogeneous trends were observed, both in presentation and in sequence for all the items studied.

In 2003, the prevalence of asthma ranged between 9.4% and 13.7%. Despite differences in methodology, this finding was consistent with Spanish data from Phase III of the ISAAC study [7]. A similar pattern was observed for chronic rhinitis, with prevalence ranging from 7.3% to 11.3%.

Consistent with the findings from the previous ORBA studies, intracountry variability and intradistrict variability were evident, as in the first edition of ISAAC [2]. This variability reaffirms the appropriateness of presenting the prevalence of asthma in a country as an epidemiological range according to different habitats and socioeconomic groups. In our study, once again, the highest rates appear in the Lycée Français, which has the highest socioeconomic level.

We observed an increase in the prevalence of asthma and rhinitis in children and adults over the 20-year study period. The yearly variation in asthma in children ranged from +0.08 to +0.31 for a prevalence ratio of 1.2 to 2.1. Data for adults were similar.

Our data contrast in part with those from Phase III of the Spanish ISAAC, which showed a stabilization in the prevalence of asthma in 13- to 14-year-olds (self-reported), with an annual variation of –0.10; the annual variation in 6- to 7-year-olds (parent-reported) took the form of a marked increase of +0.79.

Trends are not uniform throughout the world [6]. In Oceania, a decrease of –0.39 and –0.21 was observed both in the 13- to 14-year-old age group and in the 6- to 7-year-old age group; in Northern and Eastern Europe, on the other hand, increases were detected in both groups (+0.26 and +0.05, respectively). In the Mediterranean area, annual variations of –0.10 and +0.79, respectively, were recorded.

For the adult population, our data match those from Phase II of the ECRHS study [5], which was conducted with the same individuals who participated in phase I of the ECRHS 9 or 10 years previously. However, 19% and 38% of participants were lost, respectively, in each phase of the sample. The conclusion drawn was that diagnosis and treatment of asthma have improved in 5 Spanish cities.

For rhinitis, an increase in prevalence was detected in the 3 schools in relation to the 1983 and 1993 studies, with an annual variation of between +0.005 and +0.45. Von Mutius et al [8] (ISAAC III) also reported increased prevalence in children. In our study, 36% of asthmatic patients had concomitant rhinitis.

The salient weaknesses of our study are the difficulty involved in comparing our results with those of other international studies and the potential difficulty involved in extrapolating our results to other areas of Spain.

The strengths of the ORBA Project are the perfect comparability between the results from all 3 editions and the efficient use of human and economic resources. We intend to create an epidemiological observatory of asthma and chronic rhinitis in our setting.

In summary, we detected an increase in the prevalence of asthma and chronic rhinitis during the last 20 years. The factors responsible for the annual variation in the 3 schools studied were similar to those reported elsewhere [9].

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Cross-Cultural Adaptation and Linguistic Validation of the Spanish Version of the Drug Hypersensitivity Quality of Life Questionnaire

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Palabras clave: Adulto. Alergia a medicamentos. Calidad de vida relacionada con la salud. Cuestionario. Reacciones adversas a medicamentos.

Adverse drug reactions (ADRs) are a major problem in developed countries. In a prospective cohort study of outpatients followed in primary care, 25% of participants reported ADRs, 13% of which were severe [1]. It has been estimated that ADRs account for 3% to 6% of all hospital admissions and that they occur in 10% to 15% of hospitalized patients [2]. Approximately 5% to 10% of ADRs are mediated by the immune system. These are known as drug hypersensitivity reactions (DHRs) or allergic reactions. Tong et al [2] found that the incidence of DHRs in hospitalized patients was 0.42%, while the incidence of DHR during hospitalization was 0.20%.

DHRs are increasingly frequent and hamper appropriate treatment for a growing number of patients. They are the third most common reason for consultation in allergy departments after rhinitis and bronchial asthma [3]. Experiencing a DHR can leave a patient fearful about taking drugs and substantially affect quality of life (QOL).

Little research has been done into how DHRs affect QOL, in part because of the lack of instruments available to specifically assess the effect. The Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) was recently developed by an Italian research group to study the effect of drug allergy on QOL [4]. Here, we describe the adaptation and linguistic validation of the Spanish-language version (for Spain) of the DrHy-Q.

The first stage in the process was to produce a Spanish-language version of the DrHy-Q that was conceptually and semantically equivalent to the original Italian version. Two forward translations were produced by 2 experienced translators (native speakers of Spanish and fluent in Italian) working independently. A first reconciled version was produced in a meeting between the 2 forward translators and the project

DrHy-Q

Las reacciones adversas a los medicamentos pueden afectar al bienestar psíquico y/o físico de las personas. Por favor, indique el nivel de dificultad que le causa este problema

		En absoluto ▼	Poco ▼	Bastante ▼	Mucho ▼	Muchísimo ▼
1.	Como no tolero bien los medicamentos, cualquier enfermedad me limita más que a otras personas que no tengan ese problema	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2.	Me da miedo que en caso de urgencia me administren un medicamento al que soy alérgico/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3.	Debido a mi problema con los medicamentos me siento asustado/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4.	El problema de las reacciones a los medicamentos me condiciona la vida	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5.	Antes de tomar medicamentos recetados por otros especialistas, me gustaría tener la opinión de un alergólogo (médico especialista en Alergia)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6.	Para mí, cualquier pequeño malestar se convierte en un problema	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7.	El hecho de no poder tomar medicamentos tranquilamente me hace sentir diferente de los demás	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8.	Debido a mi problema de reacción a los medicamentos me siento ansioso/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9.	Me gustaría tener la certeza de que para cada enfermedad existe un medicamento que puedo tomar tranquilamente	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10.	Me da miedo no poder tratar el dolor	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11.	Debido a mi problema de reacciones adversas a los medicamentos me siento angustiado/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12.	Me preocupo cada vez que tengo que tomar un medicamento, aunque no sea el que me ha provocado la reacción alérgica	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13.	A causa de mi problema, renuncio a momentos de ocio (deporte, vacaciones, viajes, etc.)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14.	Debido a mi problema de reacciones a los medicamentos me siento desanimado/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15.	La idea de tomar un medicamiento me vuelve inquieto/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Figure. Final Spanish Version (for Spain) of the DrHy-Q.

coordinator. The remainder of the study team commented on the report and the reconciled version to produce a second reconciled version.

The second stage involved translating the reconciled forward version back into Italian (experienced translator, native speaker of Italian and fluent in Spanish). In a meeting with the project coordinator, the back translation was compared with the original version to detect any misunderstandings, mistranslations, or inaccuracies in the intermediate forward version and to correct as appropriate. A report on the back translation was produced and discussed by the study team. A second Spanish version of the questionnaire was produced.

The translated questionnaire was administered to a sample of patients with drug hypersensitivity to determine whether the translation (instructions, items, and response choices) was easily understood. The version could be modified to take into account patient comments, thereby leading to a third reconciled version of the instrument, which would be the definitive version, barring any changes required after proofreading.

A total of 9 participants (mean age, 47.4 years; 77.7% male) completed the DrHy-Q cognitive debriefing interviews. Participants varied in their educational backgrounds (predominantly lower educational level) and were recruited at the Allergy Unit of Bellvitge University Hospital, Barcelona, Spain.

After the forward translation, a first consensus version was produced at a meeting between both translators and the project coordinator. Only 3 minor changes were made after evaluation by the whole study team. This version was sent for back translation into Italian. A comparison of the back translation with the original led to the introduction of a further 6 minor modifications to the existing Spanish version. The Spanish version of the DrHy-Q obtained after back translation was sent to the developer of the questionnaire, who suggested only 1 change to item 15.

The Spanish version agreed on after back translation was administered to 9 patients with suspected drug allergy. The cognitive debriefing interviews showed that the DrHy-Q was easy to understand and clear. Patients were able to understand and respond to the items and relate their condition to the items. The participants completed the survey quickly and had no difficulties in deciding how to answer. Patients suggested minor changes to some items, not because they had difficulty understanding them, but to try to optimize the wording.

A final review by the whole study team was performed after cognitive debriefing, and 2 changes were introduced to take into account the suggestions made by patients, namely, to underline 1 sentence in item 1 in order to make the item clearer and to include an explanation of the word *alergólogo* (allergist), to help patients who might have problems with the term.

Clinical allergists generally believe that experiencing an allergic reaction to a drug can produce limitations in daily living, because many people now take drugs to treat daily symptoms. However, owing to fear of a reaction, many patients with a history of allergic reaction prefer to experience the symptoms and avoid taking a drug. The potential impact of this avoidance on QOL has not been quantified to date.

We decided to adapt and validate the Italian DrHy-Q in Spanish because the original questionnaire was developed using very appropriate methodology and because adaptation would reduce much of the effort involved in developing a questionnaire from the ground up. The DrHy-Q was simple and easy to administer and required only a few minutes to complete. Basing the adaptation process on international guidelines [5,6] led to a version that was also highly acceptable to the patient and easily understood by patients with a lower educational level.

Another advantage of performing the adaptation instead of designing a new questionnaire was that it would allow us to compare results obtained in different countries. Therefore, we encourage specialists from other countries in Europe to produce their corresponding validated version from the Italian source document.

Once the psychometric characteristics of the Spanish version of the DrHy-Q have been evaluated, the questionnaire

should be used to study how variables such as severity, type of drug, age, and sex influence the effects of ADRs on patient QOL.

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Cit s 3 as an Occupational Aeroallergen in an Orange Farmer

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Key words: Cit s 3 allergy. Orange tree allergy. Occupational asthma

Palabras clave: Alergia a Cit s 3. Alergia a naranjo. Asma ocupacional.

The orange tree, or *Citrus sinensis*, belongs to the Rutaceae family. It is widely cultivated across the Mediterranean coast of Spain. Cultivation of the orange tree involves various occupations, including pruning, grafting, and what farmers colloquially call "rolling" (cross-cutting the main branches to prevent the sap from flowing).

Despite widespread consumption of oranges, sensitization to *C sinensis* is rare. Most reports describe allergic reactions after eating orange or drinking orange juice or soda [1], with manifestations including oral allergy syndrome, urticaria, and dermatitis and systemic reactions such as exercise-induced anaphylaxis after ingestion [2].

The 3 major orange allergens [3,4] described to date are Cit s 1 (germin-like protein, 23 kDa), Cit s 2 (profilin, 14 kDa), and Cit s 3 (nonspecific lipid transfer protein [LTP], 9 kDa, with cross-reactivity to Pru p 3) [4].

LTPs have been widely identified as major allergens and are considered relevant vegetable panallergens in food allergy. Their involvement in occupational allergy is more limited, although cases involving LTP from *Triticum spelta* (Tri a 14) in bakers and LTP from asparagus or Rosaceae trees (peach and almond) in agricultural workers [5] have been reported.

Work-related respiratory symptoms have been recorded in people employed in removing the peel from oranges [6], and we recently described a case of occupational allergic respiratory symptoms due to orange peel allergens (Cit s 1 and Cit s 3), which are present only in the flavedo and cause bronchospasm after peeling [7]. The mite *Panonychus citri* has also been implicated as an occupational allergen affecting workers in the orange industry [8].

To date, there have been no reports of occupational allergy due to interaction with the orange tree, in which Cit s 3 acts as an aeroallergen.

We describe the case of a 21-year-old farmer with no family history of allergy. The patient's medical history revealed perennial rhinoconjunctivitis resulting from allergy to house dust mite and cat dander. For about 4 years, he had been experiencing increasingly intense recurrent episodes of dyspnea, coughing, wheezing, and contact urticaria while

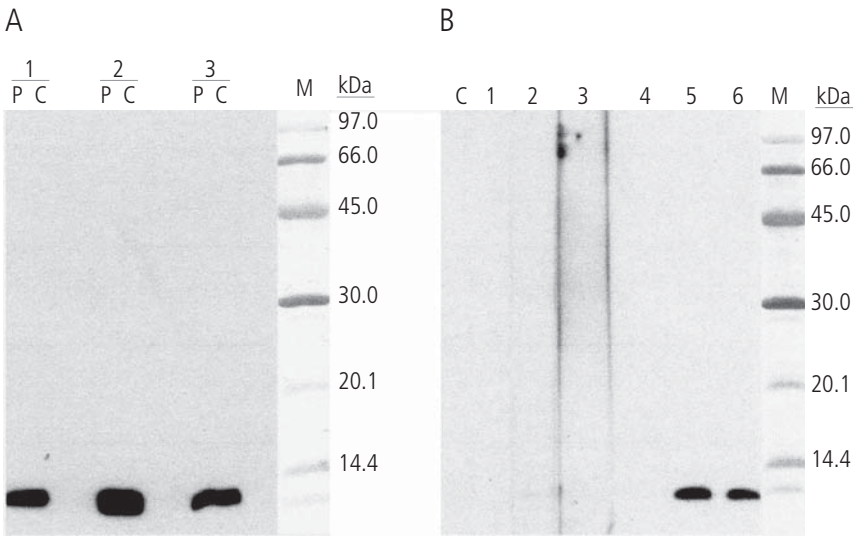

Figure. A, Sodium dodecyl sulfate polyacrylamide gel electrophoresis. Lane 1, orange leaf extract; lane 2, orange blossom extract; lane 3, orange branch extract. P indicates patient serum; C, control serum (pool of sera from nonatopic individuals).
B, Immunoblotting inhibition. Lane C, control serum (pool of sera from nonatopic individuals). Lane 1, patient serum preincubated with orange leaf extract; lane 2, patient serum preincubated with orange blossom extract; lane 3, patient serum preincubated with orange branch extract; lane 4, patient serum preincubated with peach LTP; lane 5, patient serum preincubated with BSA; lane 6, patient serum preincubated with lamb extract.

working in his fields during the months that orange trees bloom (April to July), especially when pruning, grafting, or rolling. During the rest of the year he is almost asymptomatic at work.

He tolerates handling and peeling oranges and ingestion of pulp and juice.

Skin testing for common aeroallergens in our region was positive to pollen from *Cupressus*, house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), as well as to cat dander. It was also positive for peach LTP.

We performed a prick-prick test with extract from orange tree branch, leaf, and blossom and to orange pulp and peel. The results were positive to all of them (3-mm wheal with histamine control of 3 mm). The results for the same prick-prick tests in 5 healthy controls were negative.

Baseline spirometry was performed both during the blooming season and offseason, and the results were normal. Serial measurements of peak expiratory flow rate (PEFR) during working hours outside the blooming season showed no change from the baseline measurement (560 L/min), whereas during the blooming season, the patient had a lower baseline PEFR (500 L/min), which decreased further while he was pruning and grafting, but especially when he was rolling (>20% from baseline [380-400 L/min] 2 hours after commencing work). This decrease was managed with bronchodilators and even cessation of activity.

The total immunoglobulin (Ig) E level was 600 kU_A/L.

Extracts from orange tree branch, leaf, and blossom were homogenized in phosphate buffer saline, macerated for 4 hours at 4ºC, and centrifuged. The supernatant was dialyzed in distilled water and lyophilized. Serum specific IgE to these extracts was measured using an enzyme allergosorbent test (HYTEC specific IgE EIA kit, HYCOR Biomedical Ltd) and positive levels were obtained for the 3 allergen sources (leaf, 8.0 kU_A/L; blossom, 8.3 kU_A/L; branch, 6.4 kU_A/L).

Sodium dodecyl sulfate polyacrylamide gel electrophoresis was performed using the Laemmli method [9]. IgE immunoblotting with extracts of branch, leaf, and blossom revealed 1 IgE-binding band of approximately 9-10 kDa in all of the extracts (Figure, A).

Finally, we performed an immunoblotting inhibition assay with leaf extract in the solid phase and with extracts from tree leaf, blossom, and branch and peach LTP as inhibitors (Figure, B). All of the inhibitor phases were able to inhibit the onset of the 9- to 10-kDa IgE-binding band, suggesting that the allergenic protein described was an LTP.

The orange tree is considered a low-allergenic tree owing to the entomophilous nature of its pollen. However, we showed that its aeroallergens could induce occupational allergy. Although LTPs are well known as food allergens, their aeroallergenic character has been reported in a few cases of occupational allergy. To our knowledge, this is the first report of selective sensitization to an allergen of the orange tree in a patient who experienced acute bronchospasm while performing tasks that require close contact with the tree during the blooming season. Given its molecular weight and immunoblotting inhibition results, this allergen (<14 kDa), which is found in the orange tree branch, leaf, and blossom, could correspond to Cit s 3 (nonspecific LTP, 9 kDa).

In conclusion, we demonstrated the existence of an orange tree aeroallergen with a molecular mass of <14 kDa. The aerollergen is member of the LTP family and could be Cit s 3. It seems to be responsible for the patient's work-related asthma and his contact urticaria during the months the orange tree is in bloom.

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Conflicts of Interest

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Previous Presentation

Data from this study have been presented in poster form at the XXVIII SEAIC Congress, Pamplona, Spain, October 17-20, 2012.

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Basophil Activation Test Is a Useful Tool in Occupational Asthma Due to Iroko Wood

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Key words: Basophil activation test. Iroko wood. Occupational asthma.

Palabras clave: Test de activación de basófilos. Madera de iroko. Asma ocupacional.

Occupational asthma (OA) is defined as a disease characterized by variable airflow limitation or airway hyperresponsiveness due to causes and conditions attributable to a particular work environment and not to stimuli outside the workplace [1]. It is one of the most frequent causes of work-related respiratory disease in industrialized countries [2] and is of great importance due to its clinical, socioeconomic, and medico-legal implications. Early diagnosis is therefore essential. It is estimated that around 10% to 15% of all cases of asthma are workplace related. The iroko (*Chlorophora excelsa*) is a large tree in the Moraceae family, native of West Africa. Its wood is durable and resistant to fungi, insects, and moisture, so it is widely used in hydraulics, shipbuilding, carpentry, and flooring [3].

There are few reports in the literature of OA caused by exposure to iroko wood [4-7]. The development of respiratory disease may involve immunological mechanisms, immunoglobulin (Ig) E–mediated or otherwise, and nonimmunological mechanisms, especially associated with low-molecular-weight volatile compounds, such as plicatic acid, which has been described as a toxic for the bronchial mucosa in red cedar asthma [4] and has also been implicated in immunological mechanisms other than type I hypersensitivity reactions [8]. Recently, Barranco et al [9] described a case of allergy to red cedar wood with a positive basophil activation test (BAT) against this wood.

We report the case of a 37-year-old man who had worked as a carpenter since the age of 19 and was referred from the pulmonology department to rule out allergic OA. The patient reported a 3-year history of episodic cough and wheezing due to contact with iroko wood in his workplace, with dyspnea that improved after inhalation of bronchodilators and deteriorated at night and after physical exertion. He did not experience respiratory symptoms when not in contact with iroko wood, either while working with other woods or during holidays, weekends, or rest periods. The patient also reported mild nasal symptoms during the spring.

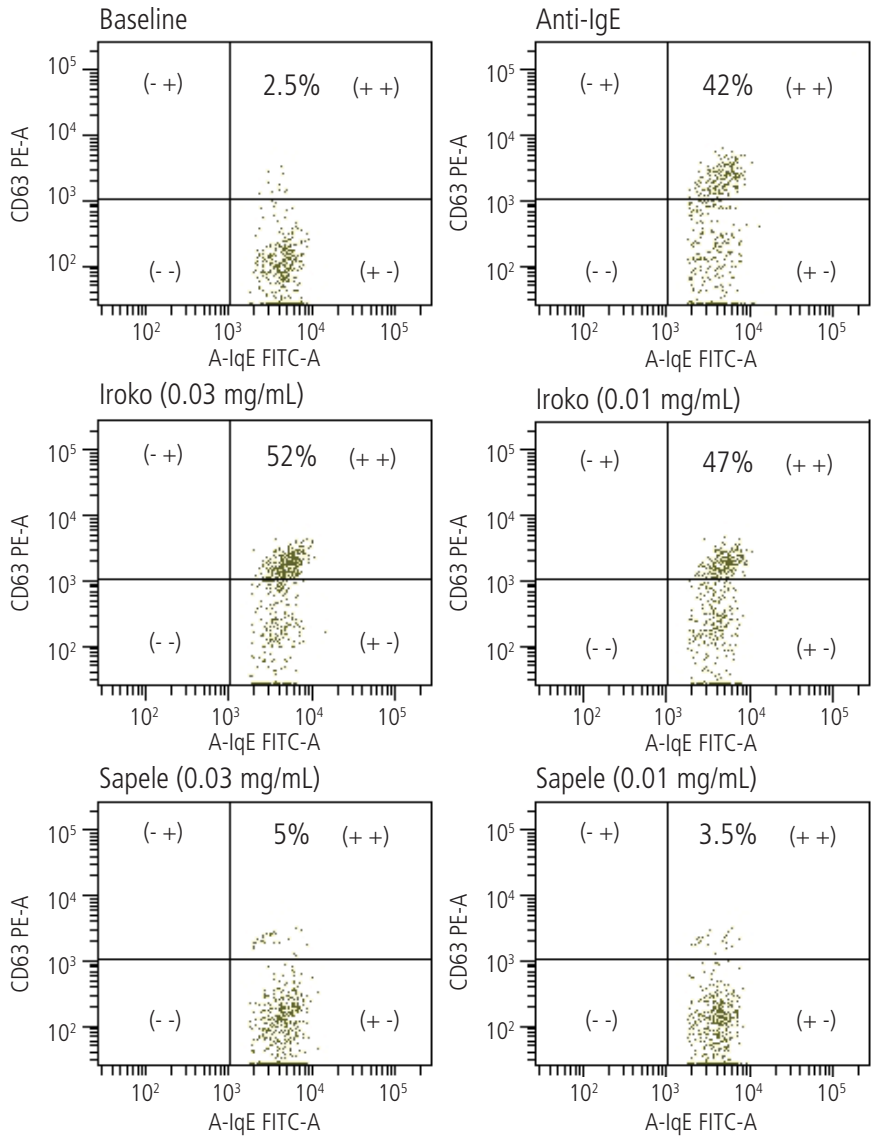

Figure. Basophil activation test (BAT) against iroko and sapele wood in a patient with suspected occupation asthma due to iroko wood. IgE indicates immunoglobulin E.

Skin tests for common aeroallergens in our region were slightly positive for mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*) and several pollens: timothy grass, cypress, olive, and *Parietaria judaica*. Total IgE was 221 kU/L, and aeroallergen-specific IgE was as follows: *D Pteronyssinus*, 0.65 kU/L; *Phleum pratense*, 2.74 kU/L; *P judaica*, 0.53 kU/L; *Olea europaea*, 3.76 kU/L; *Cupressus* species, 0.75 kU/L. Baseline spirometry was within normal limits, with a forced vital capacity (FVC) of 5.7 L (108 % of predicted), a forced expiratory volume in the first second (FEV_1) of 4.63 L (106%), an FEV_1/FVC ratio of 81.16%, and midexpiratory flow values (FEF_{25-75}) of 4.06 L (85%). The methacholine challenge test was positive (20% fall in FEV_1 from baseline [PC_{20}] at 1.16 mg/mL).

A prick test with commercial iroko wood extract (Diater Laboratorios) and a prick-to-prick test with iroko sawdust extract (10% wt/vol) were both negative. Because of the characteristics of our extracts, we decided not to perform intradermal tests, although some authors have reported positive reactions [8]. A bronchial challenge test was carried out with the same iroko sawdust after a holiday rest period. The test involved handling the dust for 15 minutes and performing subsequent serial spirometry, which showed a 13.58% reduction in baseline FEV_1 (from 4.27 L to 3.69 L) after exposure, with spontaneous recovery 30 minutes later. Subsequently, serial peak expiratory flow (PEF) rates were determined at home (baseline 600 L/min), and found to remain stable for the following 7 hours and to then decline by 8.44% after 8 hours and by 16.7% (500 L/min) after nocturnal exertion

at 11 hours, with associated wheezing and breathlessness that resolved after the administration of salbutamol (610 L/min). An exposure test conducted using the same methodology with sapele wood dust showed no immediate or late spirometry changes.

In our patient, the BAT was performed as described previously [10] with iroko extract at 2 final concentrations (0.03 and 0.01 mg/mL) using whole blood obtained from the patient and 3 controls (Figure). A positive response, ie, iroko-induced basophil activation (CD63 expression), was observed in the patient at both concentrations tested (52.2% and 47.6%), and both were negative in the 3 controls. The patient's baseline response (negative control) was 2.5% and the positive control (response to anti-IgE) was 42.8%. A BAT was also carried out with sapele wood at final concentrations of 0.03 and 0.01 mg/mL. It was negative in the basophils of both the patient and the healthy controls.

Finally, given that the result of the bronchial challenge, even though highly suggestive, does not fulfil positivity criteria (fall in FEV_1 and/or PEF of >20%), the patient was asked to return to his workplace and perform PEF registers while manipulating iroko wood and during other activities to confirm the diagnosis of OA. Serial measurement of PEF on a workday without handling iroko wood saw this parameter remain unchanged relative to the prior morning baseline measurement. Conversely, on a day involving work with iroko wood, there was a progressive decrease in serial PEF values (baseline 700 L/min) after 4 hours of exposure (590 L/min, 15.71%), reaching a peak 8 hours after onset (500 L/min; 28.57%). The patient experienced wheezing and breathlessness 2 hours after completion of the work, requiring the use of salbutamol with only partial resolution of symptoms and recovery of PEF values (630 L/min).

Following the Bernstein algorithm for the diagnosis of OA [1], we report a new case of OA induced by inhalation of tropical wood dust in an atopic carpenter, in which handling of the wood dust suggested—and serial measurements of PEF in the work environment demonstrated—the involvement of a specific stimulus, in this case iroko wood, in triggering the immediate and late bronchorestrictive response. Despite negative skin test results, which have been reported in the majority of previously described cases [5-7,9], we believe that the involvement of an immune mechanism is relevant in this process, as shown, for the first time, by a positive result in the BAT for iroko in occupational asthma.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Churg-Strauss Syndrome in a Patient Treated With Omalizumab

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Key words: Omalizumab. Asthma. Churg-Strauss syndrome. Anti-IgE. Vasculitis.

Palabras clave: Omalizumab. Asma. Síndrome de Churg Strauss. AntiIgE. Vasculitis.

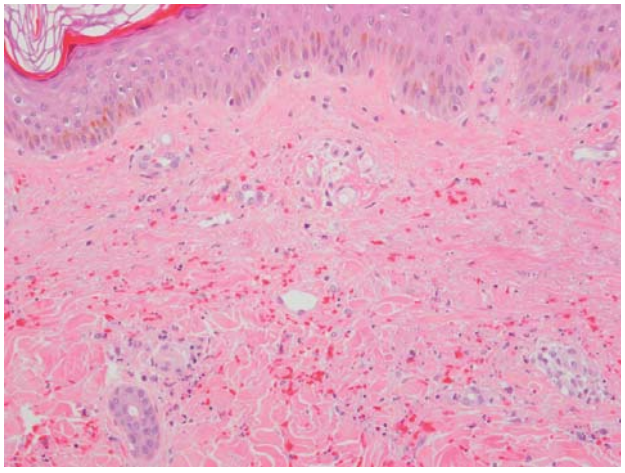

Figure. Skin biopsy showing leukocytoclastic vasculitis (hematoxylin and eosin).

Churg-Strauss syndrome (CSS) is histologically characterized by a systemic necrotizing eosinophil vasculitis affecting small- and medium-sized vessels. Almost all patients have severe, difficult-to-control, asthma. Diagnosis is confirmed by establishing the involvement of other organs, mainly the gastrointestinal tract, the heart, the skin, and the peripheral nervous system.

CSS is a rare syndrome, particularly in nonasthmatic patients. Attempts have been made to establish a relationship between the onset of CSS and the treatment of asthma, and it is postulated that the withdrawal of corticosteroids in patients with asthma as part of what has been termed formes frustes of Churg-Strauss might lead to the onset of symptoms suggesting systemic involvement of the disease [1]. This phenomenon has been previously described with other treatments used for asthma.

Omalizumab is a monoclonal anti-immunoglobulin (Ig) E antibody whose safety and tolerability have been recently reviewed [2]. It is currently included in the treatment of severe asthma, according to the global strategy for asthma management and prevention (Global Initiative for Asthma Executive Summary) [3], and has led to the reduction of doses of inhaled and systemic corticosteroids—and even their discontinuation—in patients with severe asthma.

We report the case of a 45-year old woman with a diagnosis of allergic asthma, sensitization to mites and pollen since childhood, intolerance to nonsteroidal anti-inflammatory drugs, and nasal polyps, for which she had been operated on twice. In 2003, after detection of pulmonary infiltrates on a control chest X-ray, high-resolution computed tomography showed minimal peripheral bronchial dilations and several infiltrates. Fibrobronchoscopy with transbronchial biopsy showed a preserved pulmonary structure, with focal eosinophilic infiltration and no evidence of vasculitis or granulomas. The patient had peripheral eosinophilia (7.8%-13.1%), total IgE above 600 IU/mL, and antineutrophil cytoplasmic antibodies (ANCAs) that were repeatedly negative. The initial diagnosis was uncontrolled severe allergic asthma, which required maintenance treatment with prednisone 10 mg every 2 days. In February 2007, due to a lack of control of the disease, it was decided to start treatment with omalizumab (450 mg/2 wk). At 16 weeks a very favorable therapeutic response was seen, with both clinical improvements (increase in Asthma Control Test score from 5/25 at the start of treatment to 22/25) and functional improvements (increase in baseline forced expiratory volume in the first second from 56% to 97%). The results enabled the progressive reduction and eventual discontinuation of oral corticosteroids. Three months after discontinuing oral corticosteroid therapy, the patient developed a symmetric purpuric rash on both legs. Biopsy of the lesions revealed leukocytoclastic vasculitis (Figure), confirming an initial suspicion of CSS. Due to the lack of safety information on omalizumab in this condition, treatment was discontinued. After verifying the absence of pulmonary involvement on a chest X-ray, treatment was started with 15 mg of prednisone a day for 2 weeks and all the skin lesions disappeared completely. However, 3 months after discontinuing omalizumab, the patient experienced significant impairment of her asthmatic and nasal symptoms. We recommended that she restarted treatment with omalizumab, and her asthmatic disease is now adequately controlled. She no longer requires oral corticosteroids and has had no signs or symptoms of vascular activity in 4 years.

Several reports have described a relationship between treatment with omalizumab and CSS. The first of these was published by Winchester et al [4] in 2006. As in our case, the patient exhibited clinical manifestations of CSS during treatment with omalizumab. In another case, published a year later, the authors concluded that, although treatment with anti-IgE antibodies provided adequate control of the severe asthmatic disease and a reduction in peripheral eosinophil count, it did not affect the clinical activity of CSS [5]. Similar experiences have been published [6] showing that good asthma control can be achieved in patients of this type treated with omalizumab, although it appears that the onset of CSS activity could be related to the reduction in systemic corticosteroids (the treatment of choice in this type of vasculitis) rather than to the

activation of disease by anti-IgE therapy [7]. However, Puechal et al [8] described a case of CSS in a patient not receiving oral corticosteroids prior to anti-IgE therapy and questioned the potential role of omalizumab in the development of the disease. It should, however, be highlighted that this patient had had a previous episode of giant-cell arteritis.

According to a recent safety review of omalizumab, cases of CSS reported in patients treated with this drug might correspond to cases in which the underlying syndrome would be masked by the presence of severe asthma but would then be activated on reduction or discontinuation of oral corticosteroids following improvement of the asthma [2].

A fundamental issue perhaps is the difficulty involved in diagnosing CSS, since the natural history of the disease includes several clinical stages: a prodromal stage (atopy, allergic rhinitis, and asthma), an eosinophilic stage (peripheral eosinophilia >10%, eosinophil infiltration, most frequently pulmonary), and a vasculitic stage (extrapulmonary involvement) [9]. It is currently postulated that there could be 2 different phenotypes based on whether patients are p-ANCA-positive or not, also with possible pathogenic mechanisms: ANCA-mediated vasculitis and predominant eosinophil infiltration with subsequent release of toxic products in ANCA-negative cases [10]. It is also difficult to obtain a histologic diagnosis of vasculitis by transbronchial biopsy in routine clinical practice.

In conclusion, before starting a patient on treatment, it should be checked whether or not they meet CSS criteria, although this can sometimes be very difficult to establish. In cases of confirmed or strongly suspected CSS, treatment with omalizumab would not be contraindicated, as it could provide adequate asthma control (as shown in our patient), although utmost caution should be exerted in this group of patients when reducing the dose of corticosteroids.

Our patient is monitored regularly to check for signs or symptoms of activity of disease where corticosteroid treatment would be indicated.

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Conflicts of Interest

L Herráez works at the Medical Department of Novartis Farmacéutica S.A. The rest of the authors declare that they have no conflicts of interest.

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Bleeding and Shock in a 44-Year-Old Woman With Systemic Mastocytosis

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Key words: Systemic mastocytosis. Haemorrhage. Bleeding. Coagulation. Cardiovascular collapse.

Palabras clave: Mastocitosis sistémica. Hemorragia. Sangrado. Coagulación. Colapso cardiovascular.

Mast cells play a central role in allergic disease, but they are also implicated in autoimmune diseases, inflammatory conditions, and certain malignancies [1]. Mastocytosis refers to a heterogeneous group of disorders characterized by the presence of excessive mast cells in one or more tissues, with diverse clinical manifestations [1,2].

A 44-year-old woman was transferred to the intensive care unit of our general hospital because of signs of distributive shock. Her family and personal medical history was unremarkable except for intermittent vasovagal syncopes considered harmless by her family doctor but sometimes requiring intravenous fluid therapy in her rural health care center. The woman lived in a rural environment and worked on a family farm with her husband, growing raspberries in a plastic greenhouse. In the harvest period, the patient spent many hours under the plastic of the greenhouse. On one extremely hot September day, she progressively felt malaise while working, and at noon started to experience dizziness, generalized warmth, delusional speech, and palpitations. Within minutes she developed cold sweat, trembling, and clinical signs of poor vascular perfusion. Her husband called the emergency services. Hemodynamic parameters rapidly deteriorated despite fluid infusion. Orotracheal intubation was thus performed in the emergency ambulance, and she was taken to hospital where she was admitted to the intensive care unit.

Clotting tests showed very prolonged activated partial thromboplastin time (aPTT) (120" vs 30" control value) and prothrombin time (19"2 vs 11"8 control value). Blood count showed hyperleukocytosis (38×109/L), mainly due to a rise in neutrophil count (80%). Platelet and eosinophil counts were normal. The initial hemoglobin level was 17.6 g/dL. On admission, the patient presented signs of shock with a blood pressure of 75/45 mm Hg and a pulse rate of 145 beats/min. Mechanical ventilation and vasoactive medications corrected hemodynamic status. Septic and toxic shock were ruled out. No infection was documented, and there was no argument for disseminated intravascular coagulation. Repeated clotting tests in 12 hours showed, however, that the aPTT had risen to 200" and the prothrombin time to 80". The hemoglobin level dropped to 9.9 g/dL because of vaginal bleeding and diffuse bleeding at the sites of venous puncture. The echocardiogram and electroencephalogram were normal. Total-body computed tomography showed no cerebral hemorrhage or organomegaly, but a small collection of blood was noticed in the Douglas sac. The patient's medical records revealed that she had not received any anticoagulant treatment. The coagulation test abnormalities were attributed to endogenous heparin-like factor production. This hypothesis, combined with the initial symptoms, led us to investigate a possible diagnosis of systemic mastocytosis. The patient was then also treated with fresh frozen plasma and red cell transfusions, combined with intravenous corticosteroids and H_1 and H_2 antihistamines. The aPTT and prothrombin time normalized within 3 days.

Complementary workup revealed diminished bone mineral density. A comprehensive allergic workup, including skin prick testing and total and specific immunoglobulin (Ig) E, was performed. Prick testing with foods and common inhalants was negative. Total serum IgE level was 16 IU/mL. Serum specific IgE was negative for *Anisakis simplex*, *Ascaris lumbricoides*, *Echinococcus granulosus*, *Polistes* species, *Polistes dominula*, *Dolichovespula arenaria*, *Vespa crabro*, *Vespula* species, *Bombus* species, *Apis mellifera*, raspberry, strawberry, and *Artemisia vulgaris*, and positive (0.47 KU/L) for *Olea europea*.

Systemic mastocytosis was confirmed by a serum tryptase level of up to 45.30 μg/L (normal <13 μg/L) and a bone marrow biopsy showing multifocal infiltrates of over 25% abnormal spindle-shaped mast cells. The c-kit mutation D816V (A7176T) was demonstrated in all analyzed cells (mast cells, eosinophils, $CD34^+$ cells, monocytes, granulocytes, and lymphocytes). The serum tryptase level was over 40 μg/L on day 15. All the mast cells showed the aberrant $CD25^{++}$, $CD2^{+/++}$het phenotype. The patient was discharged on day 25 with ranitidine, cetirizine, sodium cromoglycate, and alendronate. At the last follow-up visit she was still asymptomatic under the same treatment.

Systemic mastocytosis, a rare disease with abnormal growth and accumulation of mast cells in different organs, can have a benign or indolent course, or it may be associated with invalidating or even acute life-threatening symptoms such as cardiovascular collapse [1,2]. The diagnosis of systemic mastocytosis is based on known World Health Organization criteria [3]. Measurement of serum tryptase is a good screening test, since almost all patients with systemic mastocytosis have serum tryptase levels exceeding 20 ng/mL [2]. The clinical pattern depends on mast cell burden in different organs and the release of clinically relevant mediators such as histamine, leukotrienes, tryptase, and heparin [1,2].

Blood coagulation kinetics may be altered due to fibrinogenolytic and anticoagulant activities of tryptase and heparin, respectively [4]. It is known that the bullous lesions of urticaria pigmentosa may bleed, and petechiae and ecchymosis can be seen in the skin of patients with diffuse cutaneous mastocytosis [5-6]. However, coagulation alterations as severe as those seen in our patient have been infrequently reported in the literature, although there have been cases with fatal or near-fatal outcome. Furthermore, severe bleeding may complicate diagnosis and treatment in the emergency

room [7-9]. Nevertheless, severe bleeding is rare. No major bleeding events were reported in a recent review of cases of mastocytosis and mast cell activation syndromes in Spain [10]. In our patient, bleeding contributed to distributive shock and required replacement of red blood cells.

The diagnosis in our case was delayed probably due to the underestimation of preceding syncopes. The progression of the disease and lack of blocking antihistamine treatment led to a more serious picture, which could have been fatal.

Treatment of mastocytosis is directed at both inhibiting mast cell degranulation and blocking the potential systemic effects of released secretory products. Therapy includes oral disodium cromoglycate, H_1 and H_2 antihistamines, proton pump inhibitors, antileukotrienes, anticholinergics, corticosteroids, and epinephrine in the case of systemic hypotension. Treatment of systemic mastocytosis is also focused on controlling triggering factors, such as physical stimuli like heat (our case) or cold, alcohol, hymenoptera stings, or drugs such as general anesthetics or nonsteroidal anti-inflammatory drugs. Early diagnosis is essential to prevent further complications.

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Conflicts of Interest

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Omalizumab Treatment in 2 Cases of Refractory Heat Urticaria

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Palabras clave: Urticaria por calor. Omalizumab. Angioedema. Anti-IgE. Calidad de vida.

Localized heat contact urticaria or heat urticaria is a form of physical urticaria triggered by warm materials such as air, water, or various warm objects. This rare condition is one of the less common forms of physical urticaria. Avoiding heat exposure is difficult and impacts the patient's quality of life. When standard treatment is not enough, omalizumab may be considered [1]. In this article, we describe the cases of 2 patients with refractory heat urticaria treated with omalizumab.

The first patient was a 34-year-old woman with erythematous skin lesions, characterized by wheals and edema, that had appeared the previous year. The condition was clearly related to heat and appeared following exposure to both the sun (affecting exposed and unexposed parts of the body) and various heat sources (hair dryers, hot water, radiators, etc.). The patient failed to improve on antihistamines (levocetirizine, fexofenadine), montelukast, and prednisone.

In the phototest, the UV-B results were negative up to a dose of 33.31 mJ/cm^2 and the UV-A results were negative at 2.5, 5, 7, and 10 J/cm^2, with no pathological response after 24 hours. On exposure to visible light (5, 10, and 15 minutes) the minimum urticarial dose (MUD) was reached after 10 minutes. Photopatch testing with a standard photobiology set (photoallergens as recommended by the Spanish Photobiology Group; Chemotechnique Diagnostics AB) was negative.

In an open heat contact exposure test, the patient developed erythema and edema at the application site immediately after the application of hot water (53ºC) (Figure 1). A serial heat challenge test was also performed in which a glass tube containing water at progressively hotter temperatures (starting at 25ºC) was applied to the anterior aspect of the forearm. The tube was applied for 5 minutes and the result was read after 10 minutes. When there was no response (negative result), the test was repeated with a 5ºC-increase in the temperature of the water. The results were negative at 25ºC, 30ºC, 35ºC, and 40ºC, and positive at 45ºC. A Bunsen Equal-Temp 1622 circulating thermostatic bath was used for progressive heating and temperature monitoring. Two healthy controls were also challenged, with negative results.

Intradermal skin tests were also performed. The results were negative for autologous serum and plasma at room temperature (unheated) and positive for autologous serum and plasma heated to 45ºC (after standing at room temperature for 20 minutes) and for autologous serum heated to 60ºC (after standing at room temperature for 20 minutes).

Control tests performed in a patient with urticaria factitia and in 2 healthy controls were negative. The patient also underwent skin prick tests, with negative results to a set of airborne allergens, foods, *Anisakis simplex*, and latex (ALK-Abelló SA). Total immunoglobulin (Ig) E (InmunoCAP Thermo Fisher Scientific SA) was 56.8 kU/L.

The patient failed to improve on antihistamines, montelukast, H_1 antagonists, and corticosteroids, and her daily life activities were obviously limited. In view of the ineffectiveness of the above treatments and the unavoidability of exposure to the urticaria-inducing stimulus, compassionate-use treatment with omalizumab was proposed at a single dose of 300 mg/mo for 6 months. The patient improved visibly after the first dose, reduced her concomitant medication and, from the third month onwards, switched from taking her medication regularly to using it on demand. She tolerated natural exposure to heat, used heat sources (hair dryer), and sunbathed on the beach.

Figure. A, Open heat contact exposure test in patient #1. B, Intradermal test with autologous serum heated to 50ºC in patient #1. C, Open heat contact exposure test in patient #2. D, Intradermal test with autologous serum heated to 60ºC in patient #2: In bolh cases, the intradermal tests were carried out with heated serum that had been left standing at room temperature for 20 minutes.

The patient finished her course of omalizumab therapy and remained clinically stable until 3 months later, when she reported a deterioration of heat tolerance, although controllable with antihistamines.

Four months later the skin tests were repeated. The heat application test was positive at 50ºC, while the intradermal test was still negative with autologous serum at room temperature and positive with autologous serum heated to 50ºC (Figure 1).

The second patient was a 63-year-old woman who 4 years earlier had developed itchy wheals in sun-exposed areas. Since then, these lesions had recurred on exposure to the sun accompanied by heat, ie, she experienced no skin discomfort in the absence of accompanying heat (windy or breezy days or traveling in an air-conditioned car). The patient avoided exposure to the sun, which imposed limitations on her daily life, as she could not go outside during the hottest part of the day. The patient's condition failed to improve with antihistamines (ebastine, hydroxyzine), montelukast, and deflazacort.

In an open heat contact exposure test, the patient developed erythema and edema at the application site immediately after the application of hot water (53ºC) (Figure 1).The serial heat challenge test was positive at 50ºC.

The results for the intradermal skin tests were negative for autologous serum and plasma at room temperature (unheated) and positive for autologous serum and plasma heated to 45ºC and for autologous serum heated to 60ºC. Skin prick tests were negative and total IgE was 14.7 kU/L.

Because antihistamines and montelukast failed to improve the patient's condition, she was started on omalizumab at the same dose as patient #1. After the first dose there was a marked clinical improvement, with tolerance to heat exposure and no need for symptomatic treatment on a daily basis. The patient completed the 6-month course of omalizumab and the tests were repeated a month later. The heat application test was negative up to 60ºC, while the intradermal skin test was still negative with autologous serum at room temperature and positive with autologous serum heated to 60ºC (Figure 1).

Heat urticaria is a rare, difficult-to-manage condition. Its etiology and pathogenesis are unknown, but various hypotheses have been put forward [2]. Fukunaga et al [3] have suggested the presence of a serum-borne, heat-activated molecule (not IgE), with a molecular weight of over 50 kDa, whose activation would promote mast cell degranulation and the release of histamine and other mediators, thereby inducing symptoms. This theory is supported by the positive intradermal reaction seen in our patients when the serum was heated to the temperature that caused lesions in the challenge test, and the absence of an intradermal reaction with the same serum not subjected to heat. Furthermore, the result remained positive when the serum was heated to 60ºC, supporting the noninvolvement of IgE.

In recent years, omalizumab has been recommended as an option in patients who respond poorly to treatment [1,4-7], do not achieve total symptom control, and/or cannot avoid the causative agent.

The mechanism of action of omalizumab in urticaria seems to go further than simply "blocking" IgE [7], and probably involves inhibition of mast cell degranulation, as the drug is effective in patients with urticaria and normal IgE levels [4,8]. It has been suggested that omalizumab treatment may regulate histamine release from basophils [9].

The patients described here were seriously affected by their condition and conventional treatments provided insufficient disease control. It was therefore decided to try off-label omalizumab. The clinical response was very good and the effectiveness of the therapy is illustrated by the fact that, in 1 case, the heat application test became negative. In the other case the test remained positive, probably because of the delay between discontinuation of omalizumab treatment and repetition of the test. It should also be noted that clinical improvement is not always directly correlated with allergy test results and laboratory parameters.

Both patients are due to undergo another course of omalizumab therapy, as recommended in various studies [10]. In case 1 (still positive) the heat application test will be repeated once this treatment has started.

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Conflicts of Interest

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