Desensitizing Oxaliplatin-Induced Fever: A Case Report

R Madrigal-Burgaleta,1 MP Berges-Gimeno,1 D Angel-Pereira,1 C Guillen-Ponce,2 ML Sanz,3 E Alvarez-Cuesta1
1Allergy Division, Ramon y Cajal University Hospital, Madrid, Spain
2Medical Oncology Division, Ramon y Cajal University Hospital, Madrid, Spain
3Department of Allergology and Clinical Immunology, Clínica Universidad de Navarra, Pamplona, Spain

Key words: Oxaliplatin. Hypersensitivity. Fever. Desensitization.

Palabras clave: Oxaliplatino. Hipersensibilidad. Fiebre. Desensibilización. ImmunoCAP.

Symptoms of hypersensitivity reactions to oxaliplatin range from cutaneous reactions, such as flushing, pruritus, and urticaria to life-threatening respiratory and cardiovascular conditions, including bronchospasm, chest pain, and hypotension [1]. Oxaliplatin-induced fever may lead to discontinuation of treatment in some patients [2]; however, fever has been reported to be an idiosyncratic reaction caused by chemotherapy and, therefore, not amenable to rapid desensitization [3].

Desensitization has been shown to be successful in small series of individuals diagnosed with oxaliplatin hypersensitivity, and patients were able to continue their treatment, which, otherwise, would have been discontinued [1,3]. We found no publications in which a desensitization protocol was used to prevent oxaliplatin-induced fever.

We report the case of a 64-year-old man presenting with fever, shivering, general malaise, and headache as the manifestations of an adverse reaction to oxaliplatin-based chemotherapy administered to treat metastatic colorectal cancer. These manifestations were not observed during the first infusions, but appeared 30 minutes after starting the 10th infusion. The symptoms recurred in the next 3 infusions despite the use of a slow infusion rate and intensified premedication with antipyretics, corticosteroids, and antihistamines. Treatment was suspended. After discontinuation of treatment with oxaliplatin, the patient tolerated all drugs involved in the reaction except for oxaliplatin. Given that the patient had undergone several ineffective lines of therapy, he was referred to our Desensitization Program in order to assess administration of oxaliplatin.

In all the reactive administrations, blood and intravenous access cultures were negative, the results of blood tests were normal, and the patient did not have any infectious symptoms. An additional allergy workup with skin testing was performed 20 days after the last reaction to minimize false-negative results, as follows [1]: oxaliplatin prick test (5 mg/mL) and intradermal tests (0.5 mg/mL, 5 mg/mL) with histamine as the positive control and diluent as the negative control. The results were negative. Specific oxaliplatin immunoglobulin (IgE) by ImmunoCAP was <0.35 IU/L (samples for ImmunoCAP were sent to ThermoFisher Scientific Phadia AB in Uppsala, Sweden). The results of the basophil activation test were positive (samples for this test were sent to Clínica Universidad de Navarra in Pamplona, Spain).

The patient was classified as low-risk (no heart or lung diseases, forced expiratory volume in 1 second >1 L, no treatment with β-blockers, mild adverse reaction) and underwent programmed in-patient desensitization according to the standardized Brigham and Women’s Hospital protocol [1]. The procedure was performed in the medical intensive care unit. The patient received only standard oncology premedication (no additional premedications with antihistamines, corticosteroids or antipyretics were added) and tolerated the final dose of oxaliplatin with no breakthrough reactions. Six additional desensitization procedures were performed in our Desensitization Program, with no breakthrough reactions. Therapy was subsequently changed owing to progression of cancer.

Fever is not considered to be a classic feature of immediate type hypersensitivity. However, onset of fever associated with oxaliplatin has been reported. This type of fever follows a specific pattern [2,4-6]: it starts during infusion of oxaliplatin or immediately after (hours, as opposed to days); it does not necessarily occur in the presence of immediate hypersensitivity symptoms such as wheals, angioedema, hypotension, or bronchospasm; it usually appears when the patient has undergone several administrations; it does not respond well to antipyretic therapy; it is self-limiting (<48 hours); no clinical or laboratory signs of infection or alteration in blood test results are recorded; and, re-exposure to oxaliplatin triggers fever despite the use of intensified premedication with antihistamines, corticosteroids, and antipyretics. In most cases, fever is accompanied by marked discomfort, which can lead to discontinuation of treatment, thus jeopardizing prognosis [2].

Ulrich-Pur et al [5] found transient pathological elevations of interleukin (IL) 6 that were clearly related to elevations in body temperature following administration of oxaliplatin. The authors refer to an as yet undefined mechanism of IL-6 release and do not state whether infusion of oxaliplatin results directly in release of IL-6 or whether the increased expression of the IL-6 is a bystander effect of another, undefined oxaliplatin-induced phenomenon. In their report on hypersensitivity reactions to monoclonal antibodies, Brennan et al [7] reported that fever was a feature of reactions that
were otherwise suggestive of type I hypersensitivity reactions (Gell and Coombs). This type of fever was also commonly observed in the absence of reactions consistent with immediate hypersensitivity, which the authors thought might be caused by on-target or off-target effects of monoclonal therapy. They also speculated that these fevers could be part of an IgE- or mast cell-mediated reaction, given that mast cells produce tumor necrosis factor α and other pyrogens.

Saif et al [4] report the case of a patient for whom fever during one infusion was observed prior to an anaphylaxis-like reaction during the following infusion. Moreover, fevers of this type seem to appear after multiple previous infusions, thus suggesting a sensitization mechanism. The impossibility of preventing these reactions using intensified premedication with corticosteroids and antihistamines, the reappearance of fever in subsequent administrations, the positive response in the basophil activation test, and the induced tolerance to the drug with a desensitization protocol lead us to suspect that these fevers could be part of an IgE- or mast cell/basophil-mediated reaction.

Nevertheless, given that the basophil activation test has not been validated for diagnosis of hypersensitivity to oxaliplatin, our findings based on this technique are not conclusive.

Standardized rapid chemotherapy desensitization protocols such as those of the Brigham and Women’s Hospital are a safe and effective therapeutic option. In patients who have experienced hypersensitivity reactions, they can be used to guarantee first-choice treatments when administered by a specially trained allergist with experience in drug desensitization as part of a multidisciplinary approach [1]. Our patient experienced fever as the only manifestation of hypersensitivity to oxaliplatin and was able to continue his therapy after assessment, tailored treatment plans, and individualized management in our Desensitization Program.

In conclusion, despite being unable to clarify the pathophysiology of oxaliplatin-induced fever, we believe that this manifestation could be considered a symptom of hypersensitivity. Therefore, we recommend referring patients who experience this type of fever to the allergy department for a complete workup. Such an approach could prevent future onset of more severe symptoms. Desensitization should be considered an optional therapeutic tool.

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Conflicts of Interest

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Previous Presentations

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References


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Ricardo Madrigal-Burgaleta
Hospital Universitario Ramon y Cajal
Servicio de Alergia
Ctra Colmenar Viejo km 9,100
28034 Madrid, Spain
E-mail: rmadbur@hotmail.com
Occupational Asthma Due to Polyvinyl Chloride and Methyl Methacrylate in a Plumber

SA Uriarte,1 M Fernández-Nieto,1,2 J Sastre1,2
1 Fundación Jiménez Díaz, Allergy Department, Madrid, Spain
2 CIBER DE Enfermedades Respiratorias, Instituto de salud Carlos III, Ministerio de Economía y Competitividad

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Polyvinyl chloride (PVC) is a thermoplastic polymer obtained by the polymerization of vinyl chloride. It is used in industry in its rigid form (eg, containers, windows, and pipes) and its flexible form (eg, cables, toys, shoes, flooring, coatings, and stretch ceilings). PVC is one of the most widely used plastics today, a fact that is reflected in the many tons consumed annually worldwide. Exposure to PVC occurs mainly in the workplace. In the 1980s, meat-wrapper’s asthma was reported to have been caused by PVC or by products of its thermal degradation [1,2].

We report the case of a 48-year-old man with no history of atopy who worked as a professional plumber for over 30 years and had consulted for progressive dyspnea and dry cough during the last 3 years. His symptoms were triggered at work and persisted outside work. The patient had never had skin lesions and never used protective clothing, gloves, or a mask at work. He has been on sick leave for 24 months with persistent symptoms and no treatment.

The plumbing products used by the patient included adhesives for plastic pipes, welded copper tubes, PVC solvents, and paint stripper. A review of the product label and safety data sheets indicated the presence of an adhesive called Tangit PVC-U, which contained PVC powder, tetrahydrofuran, butanone, and cyclohexanone. Representatives of the manufacturer confirmed this finding and informed us that the adhesive contained traces of methyl methacrylate.

In the allergy workup, pulmonary auscultation revealed decreased lung sounds, and blood testing revealed no abnormalities. Total immunoglobulin (Ig) E was <18 IU/mL. The results of specific IgE testing for isocyanates were negative, as were the results of a skin prick test with common aeroallergens. Chest radiography showed enlarged hila, spirometry readings were normal, and the bronchodilator test result was negative.

The result of the methacholine challenge test was positive: the provocative concentration that brought about a 20% fall (PC20) in forced expiratory volume in the first second (FEV1) was 8 mg/mL, and the fraction of exhaled nitric oxide (FeNO) was 16 ppb. After obtaining written informed consent, a placebo challenge was performed by exposing the patient to lactose in a 7-m³ chamber for 30 minutes. No changes in FEV1 were observed over a 24-hour period; FEV1 and peak expiratory flow were monitored hourly with a computerized asthma monitor (Amos, Jaeger), except when the patient was sleeping.

We then performed a specific inhalation challenge (SIC) with the adhesive Tangit PVC-U in order to simulate the patient’s working conditions. The patient had a late asthmatic response, with a 33% drop in FEV1 7 hours after leaving the chamber. We did not perform the methacholine challenge test after SIC, because airflow obstruction persisted and the patient required treatment with inhaled bronchodilators and corticosteroids. No change in post-SIC FeNO was recorded.

Three months later, the patient was exposed to PVC particles (60-180 μm) in the challenge chamber at a mean concentration of 0.058-0.99 mg/m³ of total dust for 30 minutes. The concentration of aerosolized particles was measured using an aerosol monitor (DustTrack Aerosol Monitor 8520, TSI). The mixture was passed from one tray to another to produce a cloud of dust. The patient had a dual asthmatic response (immediate and late), with an immediate fall in FEV1 of 17% at 30 minutes of cumulative exposure and a late response with a fall in FEV1 of 17.3% at 7 hours after exposure to the particles. In the post-SIC methacholine challenge tests (24 hours), PC20 fell to 3.3 mg/dL. No significant change was observed in post-SIC FeNO.

Two weeks later, we performed SIC with methyl methacrylate, and the patient had a dual asthmatic response, with an immediate fall in FEV1 of 22% at 2 minutes of cumulative exposure and a late response with a fall in FEV1 of 20% at 9 hours after exposure. We did not perform the methacholine challenge test after SIC, since FEV1 was <60%. The post-SIC FeNO (24 hours) increased to 48 ppb.

The time of exposure to Tangit PVC-U adhesive, PVC particles, and methyl methacrylate, was increased steadily (0.5, 1.5, 3, 10, and 15 minutes: cumulative time, 30 minutes).

We present a rare case of occupational asthma due to PVC and methyl methacrylate. Our diagnosis was confirmed using an SIC. In the methacholine challenge test, both PVC and methyl methacrylate generated an immediate asthmatic response at a higher concentration than Tangit PVC-U adhesive, which generated only a late asthmatic response. The fact that we were unaware of the presence of traces of methyl methacrylate in the adhesive (not listed on the safety data sheets) and the positive responses in the first challenge tests could have prevented us from diagnosing sensitization to methyl methacrylate. Therefore, we suggest that every effort should be made to know the exact composition of the suspect product.

The literature contains reports of occupational asthma due to the degradation PVC products or in workers handling bottle caps [1] and packaging [2-6]. This is the first case of occupational asthma due to PVC powder content in an adhesive. Clinicians should be aware that many adhesives contain acrylics, which are capable of inducing asthma [7-10].

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References


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Silvia Uriarte
Fundación Jiménez Díaz
Avda. Reyes Católicos, 2
28040 Madrid, Spain
E-mail: sauriarte@fjd.es
Angioedema is a fairly common presenting complaint in allergy, dermatology, and emergency departments, as well as in primary care centers. It should receive special attention when it affects the upper airways or face.

Diagnosis is straightforward for patients with associated urticarial lesions (49%); however, if the condition appears in isolation (11%), other possibilities should be considered [1].

A 44-year-old Bolivian woman who had been living in Spain since 2006 was referred by her primary care physician to our hospital in April 2009 with persistent edema around her right eye. The patient worked as a caregiver for the elderly in an urban setting and smoked 1-5 cigarettes a day. She had had occasional urinary tract infection, an abortion at the age of 30 years, and a sprained ankle in 2008.

Since late 2007, the patient had had persistent right palpebral and periorbital swelling with redness and mild itching, which suggested histaminergic angioedema. However, after several visits to the emergency department, where she received treatment with antihistamines, artificial tears, tobramycin-dexamethasone eye drops, and oral corticosteroids, her condition did not improve. The patient did not have rhinitis, asthma, or drug allergy.

Physical examination revealed extensive edema with erythema affecting the right orbit and eyelid (Figure).

During the first visit in April 2009, the patient underwent skin prick tests (SPT) with common aeroallergens and Anisakis simplex and patch tests with a standard battery of contactants. The results were negative. The results of plain radiography of the paranasal sinuses, thorax, and abdomen were unremarkable. Oral corticosteroids and omeprazole were prescribed for 9 days, and the patient was advised to return if her condition worsened.

The usual laboratory tests for chronic urticaria and angioedema were performed as follows: complete blood count; biochemistry; free T4 and thyroid-stimulating hormone; C3 and C4; serum immunoglobulin G (sIgG), sIgA, and sIgM; antinuclear antibodies, anti-DNA antibodies, antithyroid antineutrophil cytoplasmic antibodies; and serologic tests (hydatid cyst, feline parasites, and sIgE against Anisakis species and foods). The results of testing in July 2009 were as follows: glycemia, 242 mg/dL; cholesterol, 276 mg/dL; triglycerides, 282 mg/dL; sIgG, 1700 mg/dL; and sIgE, 59.20 kUA/L. Urinalysis disclosed a moderate yeast cell count, bacteriuria, 500 leukocytes/µL, and a glucose concentration of 1000 mg/dL. Testing for IgE against Anisakis simplex was negative. The results of the remaining tests were within the reference range.

Subsequent treatment comprised a diabetic and lipid-lowering diet, daily monitoring of blood glucose, paracetamol for fever and pain, metformin-sitagliptin, and monitoring by an endocrinologist and family physician.

At this point, the patient was diagnosed with persistent edema that was unresponsive to conventional treatment, new-onset diabetes, and mixed hyperlipidemia, although no conclusive results were found with respect to allergic causes. Therefore, we decided to perform a skin biopsy (periorbital area), which revealed a large number of Demodex folliculorum (November 2009).

Both oral and topical metronidazole were added to the patient’s habitual treatment for 3 weeks (500 mg tid and 1 application bid on the affected area), and the angioedema disappeared after 6 weeks. The patient was followed until September 2011. During this time, she had to take a further 2 courses of antibiotics because of relapses that were closely related to poor control of diabetes. In February 2010, she remained asymptomatic while continuing to take antidiabetic drugs.

Persistent focal angioedema allows us to rule out several diseases, such as C1 inhibitor deficiency, angiotensin-converting enzyme–induced angioedema, angioedema induced by physical factors (eg, pressure), estrogen-induced angioedema, facial angioedema with eosinophilia, and idiopathic angioedema. Once these clinical conditions have been ruled out, we can consider other, less frequent conditions, namely, edema due to hypoproteinemia (observed in patients with heart disease), myxedema (hypothyroidism), lymphedema, superior vena cava syndrome, Melkerson-Rosenthal syndrome, and edema associated with soft-tissue infections [1-3].

In the present case, most of the potential causes of isolated angioedema were ruled out based on the clinical history and
the results of complementary tests. A subsequent skin biopsy confirmed an infectious origin, namely, blepharitis due to *Demodex folliculorum*.

Furthermore, we were able to rule out the involvement of sitagliptin in the onset of angioedema because the lesion had been present since late 2007 and this drug was introduced in July 2009 after the patient was diagnosed with diabetes. In addition, the patient has remained asymptomatic since February 2010 while continuing to take sitagliptin [4].

Infectious blepharitis can be caused by bacteria (*Staphylococcus* species), fungi (*Candida* species), and ectoparasites, which include head lice, *D folliculorum*, and *Demodex brevis* [5].

*D folliculorum* is a mite of the Demodicidae family measuring 0.3-0.4 mm in length. It was discovered by Henle and Berger in 1841 and described in detail by Simon in 1842. It is located mainly in the infundibular portion of the pilosebaceous follicles and in skin areas with numerous sebaceous glands (forehead, meibomian glands of the eyelid, and root of the eyelash). It can also be found in the skin of the chest, armpits, and pubis [5,6].

These parasites rarely cause disease in the skin of humans and other mammals, although they can be responsible for pityriasis folliculorum, rosacea-like demodicidosis, and blepharitis [5-10].

*D folliculorum* has been found in asymptomatic individuals, although its incidence increases with age and in patients with chronic conditions such as diabetes and immunodeficiency [5,8-10].

Diagnosis [5-8] is confirmed by direct observation of the parasite in biopsy specimens or eyelashes under optical microscopy (×40 and ×100). Indirect signs revealed using a slit lamp may also aid diagnosis (eg, plastic-like cuffs encircling the base of the eyelash and scabs).

The many drugs proposed for treatment include yellow oxide of mercury 1%, pilocarpine 4% gel, permethrin 2%, lindane 1%, and metronidazole 2%, although the results of treatment are variable [5-10]. In the present case, treatment with topical and oral metronidazole was effective.

In conclusion, C1 inhibitor deficiency must be ruled out in patients presenting with isolated angioedema. However, Melkerson-Rosenthal syndrome and edema resulting from soft tissue infection should be considered in cases of permanent angioedema affecting the face. Finally, *D folliculorum* infection must be borne in mind for patients with chronic eye conditions (blepharitis), systemic diseases (immunodeficiencies and diabetes), and age over 35-40 years.

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**References**


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**Ana Isabel Escudero Pastor**

Calle Puerta Nueva, 8, 5th B 30001 Murcia, Spain

E-mail: anaiescuderop@gmail.com
Knowledge of Anaphylaxis Among Ibero-AmericanPhysicians: Results of the Ibero-American OnlineSurvey for Physicians on the Management andTreatment of Anaphylaxis (IOSPTA) - LatinAmerican Society of Allergy, Asthma & Immunology(LASAAI)

D Solé,1 JC Ivancevich,2 V Cardona3
1Division of Allergy, Clinical Immunology and Rheumatology,Department of Pediatrics, Federal University of São Paulo,São Paulo, Brazil
2Division of Immunology, Medical School, Universidad delSalvador, Buenos Aires; Division of Allergy and Immunology,Clínica Santa Isabel, Buenos Aires, Argentina
3Section of Allergology, Department of Internal Medicine,Hospital Universitari General Vall d’Hebron, Barcelona,Spain

Key words: Epinephrine. Tryptase. Emergency department. Autoinjector


As anaphylaxis is a potentially fatal disease and can affect anyone, anywhere, familiarity with the early signs and symptoms of this condition and the ability to implement immediate emergency care must be widespread among health professionals and others who may be involved in the first-line care of patients with anaphylaxis [1].

In 2011, the World Allergy Organization (WAO) published guidelines on the assessment and management of anaphylaxis [1] in response to the lack of international recommendations on the management of this disease and the fact that certain essential drugs, supplies, and equipment for the evaluation and treatment of patients with anaphylaxis are not universally available [2]. Since their publication, the WAO guidelines have been disseminated at medical events worldwide in order to enhance awareness among health professionals potentially involved in the management of patients with anaphylaxis, regardless of whether or not they are allergy-immunology specialists (AISs). Studies have shown that knowledge of anaphylaxis is deficient and have highlighted the need for specific and targeted actions to improve it [3].

The Online Latin-American Survey of Anaphylaxis investigated patients with an anaphylaxis episode who had been referred to an AIS. Although over 90% of patients had been attended to at a hospital, only 37.3% had been treated with parenteral epinephrine [4]. These findings led us to inquire about the level of knowledge among Latin American AISs and nonspecialists regarding the recognition, diagnosis, and treatment of anaphylaxis.

The Ibero-American Online Survey for Physicians on the Management and Treatment of Anaphylaxis (IOSPTA) (online questionnaire, 10 questions), posted on the Latin American Society of Asthma Allergy and Immunology’s (LASAAI) website [5], was answered between April 20 and June 4, 2012 by 510 physicians (AISs and nonspecialists) from 22 countries in Latin America and the Iberian Peninsula (Argentina, Mexico, Brazil, Venezuela, Chile, Peru, Colombia, Spain, Ecuador, Paraguay, Bolivia, El Salvador, Guatemala, Panama, Uruguay, Dominican Republic, Portugal, Cuba, Nicaragua, Honduras, Belize, Costa Rica), as well as the United States. Data were presented as frequency of positive responses. The values obtained were analyzed according to whether the physician was an AIS or not and to whether he or she worked in emergency care. According to the nature of the variables, parametric (t test) or nonparametric ($\chi^2$ or Fisher exact test) tests were performed. The level of rejection for the null hypothesis was 5%.

The Table presents the main findings of our survey. AISs reported that they had attended patients with anaphylaxis more frequently than nonspecialists. Insect stings, foods, and drugs were the most frequently reported causes in both adults and children [1,4], highlighting the importance of training primary school teachers in the early recognition and initial treatment (eg, use of an epinephrine auto-injector) of anaphylaxis. Studies performed in schools where primary school teachers knew that they had allergic students have shown that less than a quarter of teachers had read about anaphylaxis, less than 10% knew how to use an epinephrine auto-injector, and only 6% of schools had an action plan for initial treatment [6]. This reinforces the importance of ensuring that everyone potentially involved in assisting a patient with an acute episode of anaphylaxis has the necessary knowledge.

Although measurement of total serum tryptase levels is the most important laboratory test for the diagnosis of acute anaphylaxis [1,2], only 72% of AISs identified it as such. Perhaps this is because the test is only available in 37% of the countries that participated in the initial survey conducted by the WAO [2]. However, regardless of the availability or otherwise of the test, it is expected that AISs should know about this assay.

Intramuscular (IM) epinephrine is indicated as the first-line treatment for anaphylaxis. Although there are no evidence-based recommendations, epinephrine is recommended by all guidelines as a life-saving first-aid treatment for this condition. Epinephrine, however, is underused [1,7,8]. In our study, only 71% of AISs prescribed IM epinephrine as first-line treatment. However, if we also count AISs who reported using subcutaneous epinephrine, the frequency of epinephrine use would reach 91%. Furthermore, 12% of AISs recommended the administration of epinephrine only for patients in shock, and less than half of nonspecialists indicated IM epinephrine as an initial treatment for anaphylaxis. Similar results have been observed in other health professionals [3,7]. These data allow us to conclude that knowledge of the administration of epinephrine in anaphylaxis among hospital doctors (still) appears to be deficient. Epinephrine auto-injectors are widely available in Belize, Spain, Portugal, and the United States.

Consensus is lacking on the use of H2-antihistamines, H1-antihistamines, or corticosteroids as the recommended initial treatment of anaphylaxis [9,10]. Nevertheless, and particularly among nonspecialists, prescription of corticosteroids was recommended by almost one-third of the physicians assessed in our survey.

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To prevent dual-phase anaphylaxis [1], 91.7% of AISs and 83.1% of nonspecialists recommended that patients with an acute episode remain in observation for 6 to 12 hours. Nevertheless, it is intriguing that 6.6% of AISs recommended this action only for patients with anaphylactic shock and hypotension.

In conclusion, our survey shows that knowledge of anaphylaxis recognition, diagnosis, and treatment must be enhanced among physicians and also among AISs, and that it should be extended to anybody directly involved with groups of people, particularly in areas where anaphylactic reactions may be common, such as schools. The dissemination of the WAO guidelines on anaphylaxis should be everyone’s job.

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Conflicts of Interest
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Seafood allergies, including those caused by fish and crustaceans such as *Marsupenaeus japonicus*, are among the most common food allergies [1]. One of the most prevalent allergens identified—parvalbumin—has been reported to be present in fish and amphibian species as well as in crustaceans. Parvalbumin is therefore considered the main panallergen in seafood allergy [2]. Furthermore, tropomyosin has been described as a major cross-reactive allergen in the subphylum Crustacea. Other known crustacean allergens are creatine kinase, myosin light chain, and sarcoplasmic calcium binding protein (reviewed in [3]). Cross-reactive tropomyosins have also been described within the phylum of Arthropoda (eg, *Dermatophagoides pteronyssinus*).

We report on a 27-year-old man (#182) who experienced angioedema, dyspnea, and urticaria following the ingestion of cooked prawns (Figure A). Although total immunoglobulin (Ig) E was 268 kU/L, specific IgE for prawn was only 0.47 kU/L (CAP-FEIA). Interestingly, high specific IgE for *Dermatophagoides pteronyssinus* (9.98 kU/L, CAP) was detected, possibly due to tropomyosin cross-reactivity, but specific IgE for the major prawn allergen Pen a 1 was low (tropomyosin, 0.21 kU/L; CAP). It was therefore decided to analyze additional putative allergens from *M. japonicus*, an important breeding prawn. We also included 2 atopic patients (#295 and #323), with atopy defined as high IgE (total IgE, >100 kU/L; CAP-FEIA) detection and at least one relevant type 1 sensitization, and one nonatopic control (#155) with no history of adverse reactions to prawn (Figure A).

Protein extracts from *M. japonicus* were separated by 2D gel electrophoresis (Figure B). Gels were blotted and incubated without sera and with sera from the prawn-allergic patient (Figure B #182) and the nonatopic (Figure B #155) and atopic controls (#295 shown in Figure B, #323 not shown). Subsequently, IgE binding was determined by specific anti-human-IgE-antibodies. The IgE-reactive proteins detected were identified by mass spectrometry [4].
Practitioner’s Corner

### A

<table>
<thead>
<tr>
<th>Patients #</th>
<th>Patient Specificity</th>
<th>Age</th>
<th>Sex</th>
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Abbreviations: AE, angioedema; D, dyspnea; IgE, immunoglobulin E; nd, not determined; U, urticaria.

### B

Figure. Identification of allergenic proteins from *Marsupenaeus japonicus*. A, Overview of patients examined including a summary of clinical symptoms and immunoglobulin (Ig) E evaluation of the sera. B, 2D gel with extracts from *M japonicus* and corresponding western blots; 200 μg of protein from *M japonicus* extracts were applied to a small (7-cm) strip for the first dimension followed by sodium dodecyl sulphate polyacrylamide gel electrophoresis using a 12% gel in the second dimension. Gels were blotted onto nitrocellulose membranes. After incubation with sera from the patients, the blots were developed with an anti-IgE antibody conjugated with alkaline phosphatase (#155 nonatopic control; #295, atopic control 1; and #182, prawn-allergic patient). Preparative gels were stained with Coomassie after electrophoresis. All proteins identified as allergens by Western blot detection are encircled. We most often found protein identities in groups (encircled in 3 and 4). C, Summary of IgE-binding proteins identified in *M japonicus*. The identified proteins are listed with the spot number taken from Figure B. Listed are the NCBI accession number, the MS/MS-Mowse Score and the number of peptides used in the Mowse search. Furthermore a summary of the signals obtained from incubation of the western blots with different proteins.

### C

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<tr>
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<td>2375</td>
<td>14</td>
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<td>13</td>
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<td></td>
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</table>

++strong signal Western blot; +weak signal Western blot.

Three IgE-reactive proteins were detected upon Western blot incubation and mass-spectrometric identification of protein spots (Figure B, spots 1-5 and Figure C). In addition to low affinity towards the known major allergen tropomyosin (spot 5 in the Coomassie-stained gel in Figure B), strong IgE reactivity was found towards pyruvate kinase and phosphopyruvate hydratase, possibly explaining the allergic reactions. In both of the atopic control patients with a history of tolerating crustaceans, specific IgE to *D pteronyssinus* was determined by CAP FEIA; tropomyosin binding, however, was detected by immunoblotting in only 1 of the patients, possibly due to cross-reactivity to Der p 1.
We have reported for the first time that pyruvate kinase and phosphopyruvate hydratase might be potential crustacean allergens. Pyruvate kinase is a cytosolic protein of about 68 kDa and, according to the 2D gel analysis, of relatively high abundance (Figure B, spots 1 and 2). Phosphopyruvate hydratase, also called enolase, is a cytosolic protein of about 50 kDa involved in glycolysis and was one of the most abundant proteins in the sample (Figure B, spots 3 and 4).

An important goal in improving the in vitro diagnosis of food allergy is to increase specificity with regard to predicting the clinical situation [5] and to gain knowledge about allergen cross-reactivity.

Several factors have been reported to play a crucial role in defining IgE binding to a protein. The first is homology between animal and human protein sequences [6]. Usually, only proteins with a homology of less than 63% with human proteins are known as allergens. Second, the abundance of a protein contributes to its allergenicity, meaning that proteins of higher abundance are more likely to be recognized by the immune system than rare proteins. This holds true for pyruvate kinase in *M japonicus*, where the protein was abundant and readily recognized by Western blot analysis (Figure B). Third, there are specific sequences that facilitate allergenicity. A theoretical allergenicity was assessed by the algorithm used in the software Evaller [7]. Tropomyosin, as a positive control, was found to be allergenic with a 0% chance of false identification. The results for pyruvate kinase and phosphopyruvate hydratase from *M japonicus* were that they were presumably not allergens, with only a 5.2% and 12.7% probability of being overlooked, respectively. This means, however, that they have only low theoretical allergenic potential. Even though the prediction of allergenic sequences has been improved thanks to knowledge of allergens already identified biochemically, computer algorithms cannot replace biochemical experiments [4]. The relevance of pyruvate kinase and phosphopyruvate hydratase as functional IgE-reactive proteins of *M japonicus* remains to be determined. Because of the known cross-reactivity of tropomyosin, more in-depth knowledge of minor crustacean allergens might help to establish a correct diagnosis.

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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Janina M. Tomm
Department of Proteomics
Helmholtz-Centre for Environmental Research
Permoserstrasse 15
04318 Leipzig, Germany
E-mail: janina.tomm@ufz.de
Anaphylaxis Caused by Flaxseed

A Álvarez-Perea, D Pérez Alzate, A Doleo Maldonado, ML Baeza
1 Allergy Department, Hospital General Universitario "Gregorio Marañón", Madrid, Spain
2 Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER) - U761

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Flax or linseed (Linum usitatissimum) belongs to the Linaceae family. It is native to the region stretching from the Mediterranean coast to India, and has been used in the production of textiles since ancient times; it is also used to extract vegetable oil and produce flour. Flaxseed derivatives can be also been found in bakery products and animal feed (birds, dogs, cats, horses, etc). Finally, in recent years, the use of flaxseed has increased dramatically in the so-called alternative medicine industry, mainly because of its laxative properties. A 61-year-old man reported an allergic reaction to flaxseed. Out of curiosity, he had ingested two linum seeds and had immediately experienced oral pruritus, vomiting, persistent abdominal cramps, dyspnea, and facial angioedema. He was treated with methylprednisolone and dexchlorpheniramine in the emergency room.

For years, he had experienced ocular pruritus when he cleaned his canary bird feeders. The patient brought bird feed to be inspected and flaxseed was found, among other seeds. He also experienced oral pruritus after eating multigrain bread.

A prick-to-prick test with flaxseed yielded positive results. Control tests performed in 3 atopic individuals produced no irritant effects. Skin prick tests were carried out with standard aeroallergens, which resulted positive for Cupressus arizonica, Fraxinus excelsior, Platanus hispanica, Olea europaea, Phleum pratense, Lollium perenne, Cynodon dactylon, Plantago lanceolata, and Chenopodium album. The results were negative for dust mites, fungi, dog and cat dander, cockroach, and feathers.

Total immunoglobulin (Ig) E (ImmunoCAP, Phadia) was 158 kU/L, and specific IgE to profilin and lipid transfer protein (LTP) was less than 0.35 kU/L. A flaxseed extract was prepared in our laboratory. Enzyme-linked immunosorbent assay (ELISA) yielded positive IgE levels for flaxseed (absorbance OD405, 0.418±0.05; control serum, 0.04±0.002).

The flaxseed extract was resolved using 12.5% sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a polyvinylidene fluoride microporous membrane. The immunoblot detected IgE-binding proteins of 25, 43, 53 and 62 kDa (Figure). Immunoblot inhibition did not reveal any relationship between flaxseed and Phleum pratense or Olea europaea.

Flaxseed has rarely been reported as a sensitizer [1]. Since 1930, only 5 cases have been reported, and 2 of these have been in the last 10 years [2-6]. Most of the cases reported involved anaphylaxis. In 1 of the reports, Leon et al [5] described a 56-kDa allergen and proposed it as a major allergen in flaxseed.

In our case, the positive prick-to-prick test and the positive IgE ELISA and immunoblot results confirmed that our patient experienced IgE-mediated anaphylaxis caused by flaxseed allergy. Additionally, the 53-kDa band detected in the IgE-immunoblot of our patient could be the same 56-kDa allergen described by Leon et al [5]. We were unable to find evidence of cross-reactivity to pollens (Phleum pratense and Olea europaea) or sensitization to other panallergens, such as profilin and LTP. Prior to the episode, the patient had had minor symptoms following contact with other sources of flaxseed (bird feed and multigrain bread).

Given the growing use of this seed in many industries, including food and alternative medicine, an increase in allergic reactions is to be expected and flaxseed should be considered in the investigation of patients with suspected allergic reactions to cereals and other grains.

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References


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Alberto Álvarez-Perea
Servicio de Alergia
Hospital General Universitario Gregorio Marañón
C/ Doctor Esquerdo 46
28007 Madrid, Spain
E-mail: alberto@alvarezperea.com