That Simulates Allergic Diseases

Strongyloidiasis: An Emerging Infectious Disease That Simulates Allergic Diseases

1 Allergy Unit, Hospital General Universitario, Valencia, Spain
2 Microbiology Department, Hospital General Universitario, Valencia, Spain

Key words: Strongyloidiasis. Eosinophilia. Chronic cough

Strongyloides stercoralis is an intestinal parasitic nematode that is present around the world and endemic in rural areas with tropical or subtropical climates [1]. In Spain, cases of infection have been described along the Mediterranean coast [2], in Zaragoza [3], and in southern Galicia [4]. A risk factor for infection in our country is agricultural work in wetlands or rice fields [2].

We present the case of a nonsmoking 27-year-old man of Bolivian origin who reported nonseasonal symptoms of 1-year duration consisting of expectoration that caused coughing every morning but was nonproductive throughout the rest of the day. He also experienced episodes of exacerbated symptoms with an intensely itchy throat and a feeling of mucus in the throat, although he reported that it primarily produced saliva. There was no fever. He was referred to our department to rule out an allergic cause.

Laboratory tests showed a total immunoglobulin (Ig) E level of 5000 kU/L and eosinophilia (700 cells/μL); serum determinations of specific IgE antibodies were positive for dust mites (Dermatophagoides) (1.42 kU/L), Poaceae (Cynodon dactylon, 7.82 kU/L; Phleum pratense, 4.46 kU/L), Parietaria judaica (3.12 kU/L), and Olea europaea (3.12 kU/L), but negative for dog and cat dander and Alternaria alternata. The patient reported that his symptoms had not improved despite daily treatment with oral antihistamines (ebastine 20 mg) for several months and inhaled budesonide at 400 μg every 6 hours, which had been prescribed just 24 hours before his first visit.

Due to the high levels of total IgE and the presence of eosinophilia, we ordered a stool test for parasites, and added omeprazole 40 mg per day to budesonide every 8 hours to evaluate its therapeutic effect. On receiving the request for a stool test in a Bolivian patient with such high IgE levels, the microbiology laboratory asked for new stool samples without preservatives to test for S. stercoralis larvae. Several rhabditoid larvae were observed in the stools by optical microscopy and abundant filariform larvae were found in the 24-hour agar-plate culture, which is a more sensitive method in which larger samples are analyzed. When informed of the positive results for strongyloidiasis, we immediately withdrew the inhaled budesonide and referred the patient for urgent evaluation at the International Medicine Unit of the Infectious Diseases Department at Hospital General Universitario de Valencia to initiate treatment (ivermectin at 200 μg/kg/d for 2 days).

On questioning the patient to find a possible source of exposure to the parasite, he reported having walked barefoot as a child through agricultural areas and standing water.

Autoinfection with S stercoralis is a chronic disease that can last for decades if the infected person’s immune system is intact [1,5]. It can be clinically invisible (in up to half of cases the only sign is fluctuating eosinophilia) or it may manifest itself through symptoms that appear only when the larvae migrate. These include cutaneous symptoms (burning, urticaria, and pruritus in the area penetrated by the larvae); gastrointestinal symptoms (epigastralgia, indigestion, intermittent mucous diarrhea, chronic malabsorption); and respiratory symptoms (cough, fever, hoarseness, and bronchospasm) [1,4,5].

Humans become infected when the larva penetrates the skin of the hands, feet, or back in its filariform state (L3). It then enters the circulatory system and reaches the lungs, from where it is coughed up and swallowed. Once in the intestines it matures into a parthenogenetic female that lays eggs that hatch into rhabditiform larvae (L1) that are excreted in feces to complete their cycle in the soil, where they await another host [4]. Some L1 larvae can mature into L3 larvae and, through the colonic mucosa or the perianal skin, cause endogenous autoinfection that produces few symptoms [1].

Diagnosis is established by detection of rhabditoid larvae in stools, and filariform larvae can be seen in a 24-hour agar culture. The parasite load is low, and larval expulsion to the outside environment is very irregular. A simple stool test can fail in up to 70% of cases [5,6].

Depending on the state of infection, the parasite can be found, in all stages of its lifecycle, in bronchoalveolar lavage fluid [3] cerebrospinal fluid, urine, blood, gastric fluid, and peritoneal lavage fluid [6].

A number of enzyme-linked immunosorbent assays have recently proven to be useful for diagnosis and posttreatment evaluation, although they are less effective in patients with hematological malignancies or HTLV-I infection [7]; they also show cross-reactivity with hookworms, filariae, and schistosomes [6].

Most cases of severe S stercoralis infection occur in patients who have been taking corticosteroids for over a year [5,7,8]. It has been reported that corticosteroid doses of over 0.3 mg/kg/d can facilitate the loss of T lymphocytes from the circulation, thereby disrupting their ability to reach the site of infection [6]. It is also known that corticosteroids accelerate the maturation of S stercoralis larvae in the intestine, suppress eosinophilia [7], and reduce local inflammation, thus eliminating another barrier to the migration of this parasite [6].
A considerable number of cases of disseminated strongyloidiasis reported in the literature have been in patients with chronic obstructive pulmonary disease. In such cases, the respiratory symptoms of strongyloidiasis can be masked by the pre-existing bronchial disease, leading to delays in diagnosis and in initiation of appropriate treatment [9].

Because of current immigration trends and the persistence of this parasitic infestation, which can last for years or even decades, we believe that it is important to alert allergy specialists in settings such as ours to the possibility of an increase in cases. The frequent administration of corticosteroids in patients treated in our offices increases the risk of hyperinfection, a severe complication associated with a mortality of around 80% [7,10].

We stress the importance of testing for strongyloidiasis when eosinophilia is observed in a patient who is from a disease-endemic area or who has a history of working in wetland areas [2,3,8]. Particular attention is required in patients who require immunosuppressive or corticosteroid therapy [10].

As a microbiological diagnosis cannot be made with standard stool examination, the laboratory should be advised of the possibility of strongyloidiasis and sent stool samples without preservatives or refrigeration [4,5]; strongyloides serology should also be ordered. If the stool studies are negative and clinical suspicion persists, the patient should be followed up with repeated stool studies, especially when serology is positive [5,7].

References
Urticaria-Angioedema Due to Carboxymethylcellulose Eye Drops

A Carbonell,1 JC Miralles,1 AI Escudero,1 A Martínez,1 F Pineda,2 D Aldana2
1 Allergy Section, Hospital General Universitario Reina Sofía. Murcia
2 I+D Diater Laboratory, Madrid, Spain

Key words: Strongyloidiasis, Eosinophilia, Chronic cough
Palabras clave: Strongyloidiasis, Eosinofilia, Tos crónica

Carboxymethylcellulose (CMC) is a synthetic polymer, soluble in water, in which CH2COOH groups replace glucose units on the cellulose chain through an ether bond. Its molecular weight ranges from 21 kDa (low-density CMC) to 500 kDa (high-density CMC). The product is the sodium salt of carboxylic acid. CMC is formed from cellulose (the main polysaccharide constituent of wood and all plant structures) through a reaction between alkaline cellulose and chlorine sodium acetate. It can be produced commercially by the chemical modification of wood. The commercial product is soluble in water and comes as colorless, odorless powder or granules.

CMC has very diverse uses. It is used mainly as a thickening agent, but also as a filler, dietary fiber, an anti-clumping agent, and an emulsifier. It is found in detergents, soaps, cosmetics and pharmaceutical products, and foodstuffs (in which it is used as a thickener, a binder, a suspension agent, and a stabilizer); it is also used in paper, cardboard, and textile manufacturing.

There have been reports of anaphylactic shock following the administration of CMC in corticosteroid injections [1-4] and barium sulfate suspensions [5,6]. CMC is also used as a tear-replacement product in the treatment of dry eye syndrome [7] and has been known to cause contact allergic dermatitis in this setting [8]. To the best of our knowledge, however, there have been no reports of a type I hypersensitivity reaction to CMC in an ophthalmic solution.

We present the case of a 44-year-old man, a sweeper by profession, with a history of high blood pressure under treatment with ramipril. Several weeks earlier, he had been prescribed an eye drop called Viscofresh (CMC) to treat a sore eye. Immediately after applying the drops, he developed intense conjunctival erythema and bilateral periorcular edema with urticarial lesions on the face and trunk. He went to the emergency room, where he was administered methylprednisolone and dexchlorpheniramine intramuscularly and instructed to continue oral treatment for 5 days, until complete remission of the clinical manifestations.

The patient commented that 6 months before the reaction he had developed generalized urticaria, without angioedema or respiratory distress, immediately after a lumbar epidural infiltration with Trigon Depot (triamcinolone + Tween 80 + CMC + benzyl alcohol) and bupivacaine to treat left lumbosacral pain (discopathy L5-S1). He had been treated with intramuscular methylprednisolone and dexchlorpheniramine, and responded well, although some of the lesions lasted for 2 days.

In our evaluation of the patient, we performed skin prick tests (SPTs) with Viscofresh drops (CMC) at a concentration of 5 mg/mL and Trigon Depot at a concentration of 40 mg/mL. The results were positive in both cases (and negative in 5 controls). SPTs with Tween 80 and benzyl alcohol were negative, as were an oral challenge with triamcinolone and a subcutaneous challenge with bupivacaine.

We used the dot blot technique described by Towbin et al [9] to test for the presence of specific immunoglobulin (Ig) E to CMC. This technique, which is used to detect, analyze, and identify proteins, differs from the Western blot technique in that protein samples are not separated electrophoretically but are spotted directly onto a membrane or paper substrate through circular templates. Once the samples had been spotted onto the polyvinyl difluoride membrane at the center of the grid, the membrane was left to dry and nonspecific sites were blocked by soaking in 1% bovine serum albumin in phosphate-buffered serum (PBS)-Tween 0.5%. The primary antibody (patient serum) and then the secondary conjugated antibody (anti-IgE) were incubated with an enzymatic marker that emits a signal, collected on photographic film, when it comes in contact with another reagent (in our case, a luminescent agent).

The dot blot showed that the samples of Viscofresh (CMC) undiluted and diluted at concentrations of 1:2, 1:4, and 1:10 in 1% BSA in PBS-Tween 0.5% reacted with the patient’s serum, whereas there was no reaction with the atopic control serum (Figure). There was no recognition of serum when only blocking buffer was added to the dot (negative control for technique). We can therefore conclude that CMC was specifically recognized by the patient’s serum.

We have presented a case of a patient who developed urticaria and angioedema following the administration of CMC as eye drops, and have proven, using SPTs and laboratory tests, that the reaction was IgE-mediated. It is worth noting that a
few months earlier, the patient had also developed a urticarial reaction to a corticosteroid injection containing sodium CMC. To our knowledge, this is the first report of an IgE-mediated urticarial reaction after the administration of CMC as eye drops.

References


Salmonella Vertebral Osteitis and Sepsis in a Girl With Interferon Gamma Pathway Deficiency

CT Quezada Chalita,1 L. Blancaz Galicia,2 L. Jannière,3 G García,4 M Moncada Velez,2 D Pietropaolo Cienfuegos,1 B del Río,1 JL Casanova,5,6 S Boisson-Dupuis,1 J Bustamante,1 SO Lugo Reyes2

1 Clinical Immunology and Allergology Department, “Federico Gomez” Children’s Hospital, Mexico City, Mexico
2 Immunodeficiencies Research Unit at the National Institute of Pediatrics, Mexico City, Mexico
3 The Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U980, Necker Medical School, Paris, France
4 Pathology Department at the “Federico Gomez” Children’s Hospital, Mexico City, Mexico
5 St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY, USA

Key words: Salmonella osteitis. Mycobacteria. Primary immunodeficiencies. Interferon gamma.

Palabras clave: Osteitis por salmonella, micobacteria, immunodeficiencia primaria, interferon gamma.

Primary immunodeficiency diseases are caused by congenital defects in cellular, humoral, or molecular functions of the intricate immune system. More than 160 of these defects have been described, and at least 100 genes have been incriminated [1]. Mendelian susceptibility to mycobacterial disease (MSMD) is a clinically defined, genetically heterogeneous group of primary immunodeficiencies caused by mutations in genes that code for both components of the interferon (IFN) γ-interleukin 12/23 circuit between lymphocytes and macrophages [2,3] and the respiratory burst pathway [4], thereby disrupting the immune response to intracellular pathogens. Patients are otherwise quite healthy and only rarely develop other unusually severe bacterial, viral, fungal, or parasitic diseases [5]. In practically all cases, patients are vulnerable to mycobacteria; they can develop adverse reactions to the bacille Calmette-Guérin (BCG) vaccine and infections caused by environmental nontuberculous mycobacteria. One notable exception is non-typhi Salmonella, which causes disease in approximately 50% of these patients [2,5]. To date, 8 genes (IFNGR1, IFNGR2, IL12B, IL12RB1, STAT1, IRF8, IKBA, and CYBB) and 16 genotypes have been identified as responsible for MSMD [2,3,4]. Nonetheless, the genetic etiology is unknown in approximately 50% of patients.

Here, we describe the case of a female preschool-age patient who did not react to the BCG vaccine but did develop severe disseminated Salmonella infection in association with vertebral osteitis treated with broad-spectrum antibiotics and surgical resection. Both Mycobacterium tuberculosis and Group D Salmonella were identified.

The patient was a 4-year-old Mexican girl born at term
to nonconsanguineous parents in 2006. She had received the BCG vaccine (Pasteur strain) as a newborn. At the age of 22 months, she presented with a 5-month history of neck spasticity and progressive descending weakness in her arms and legs. On physical examination, she was found to have left-sided torticollis and a small, firm, nontender posterior cervical mass. Neurological examination revealed intact cranial nerves and superficial sensitivity, but brisk tendon reflexes, as well as reduced muscular strength and a bilateral extensor plantar reflex. A pyramidal syndrome was noted, and the patient was admitted for further investigation.

Computed tomography of the neck revealed osteolytic lesions of vertebral bodies at C7 and T1 (Figure), suggestive of tuberculous osteitis of the spine (Pott’s disease). The patient underwent an excisional biopsy of the cervical mass and a posterior corpectomy. Surgical specimens had nonspecific acute inflammation, with no evidence of granuloma formation. A polymerase chain reaction (PCR) was positive for Mycobacterium tuberculosis. Furthermore, Group D Salmonella was grown from surgical specimens and serial cultures from blood. A 4-drug antituberculosis regimen was started and endovenous ceftriaxone was administered for 6 weeks.

The laboratory workup revealed leukocytosis with neutrophilia. Serum immunoglobulins, complement levels, lymphocyte subpopulations, and the nitroblue tetrazolium (NBT) reduction assay were all normal. Superoxide production by lymphoblastoid (Epstein-Barr virus–transformed) cells obtained from the patient was also normal as measured by the cytochrome-c reduction assay. Baseline plasma IFN-γ was undetectable. Whole-blood activation assay with BCG, IL-12, and IFN-γ revealed normal interferon production in response to stimulation with BCG+IL-12; low but present IL-12p40 as measured by enzyme-linked immunosorbent assay; and a lack of IL-12p70 production in response to BCG+IFN-γ [6]. Partial IFNGR deficiency was suspected on the basis of the presence of IL-12 but a lack of response to appropriate stimuli.

The patient completed 9 months of antimycobacterial treatment and is currently alive and well. No other mycobacterial or opportunistic infections have been observed. She is not receiving oral prophylaxis with antibiotics or subcutaneous recombinant interferon gamma. Genetic analysis to further characterize the defect is currently being pursued.

We have described the case of a preschool-age girl with MSMD who developed vertebral osteitis and sepsis. Both Salmonella species and Mycobacterium tuberculosis were identified from surgical specimens, and good recovery was observed after the patient received a multidrug antibiotic regimen.

MSMD was probably first described clinically in 1951, and its first genetic etiology was identified in 1996 [7]. This group of immune defects has a high degree of allelic heterogeneity and exists as recessive, dominant, or X-linked inheritance patterns and in both partial and complete forms [2]. Contrary to previous reports of MSMD [2,5], our patient’s history is remarkable in that she did not develop Mycobacterium bovis infection after administration of the BCG vaccine, and she first presented as a toddler with a severe, invasive, acute Salmonella infection, which apparently coexisted with a chronic insidious mycobacterial infection of the vertebrae caused by Mycobacterium tuberculosis.

Salmonellae are gram-negative, facultative anaerobic intracellular bacteria that usually cause foodborne gastrointestinal infections. Bacteremia develops in less than 5% of all patients with Salmonella gastroenteritis [8], and disseminated infections are only rarely seen, except in patients with acquired immunosuppression (eg, human immunodeficiency virus, rheumatoid arthritis, diabetes mellitus, patients receiving tumor necrosis factor blockers), or congenital defects (eg, Sickle-cell disease, chronic granulomatous disease, hyper-IgM syndrome, MyD88, and NEMO deficiencies) [9]. Recurrent, persistent and severe invasive Salmonella infections are seen in about 50% of patients with MSMD, especially in defects affecting the IL-12/23 loop of the IL12/23-IFN-γ circuit [8], but also in STAT1 deficiency [5]. In our patient, age at onset (2 years),
clinical presentation (multifocal vertebral osteitis), and clinical outcome (good response to antibiotics and full recovery) all suggest a partial defect in the IFNGR1, IFNGR2, or STAT1 genes. However, MSMD is defined clinically, and novel genetic etiologies are being discovered at a fast rate.

Salmonella vertebral osteomyelitis presents with several features similar to those of pyogenic vertebral osteitis due to other agents, including mycobacteria. Depending on the context, for example, in regions of the world where tuberculosis is endemic, Salmonella osteitis of the vertebrae can be mistaken for tuberculosis [10] and treated inadequately. When faced with vertebral osteitic lesions, thus, especially in a patient suspected to have MSMD, histopathology images and cultures are indispensable for the clinician to distinguish between salmonellal and mycobacterial etiologies.

Acknowledgments

The radiology and pathology departments at the Hospital Infantil de México kindly discussed and provided the image included in this report. The immunodeficiencies research unit is supported by grants from Consejo Nacional de Ciencia y Tecnología (Conacyt, grant #700502), and Fundacion Mexicana para Niñas y Niños con Inmunodeficiencias Primarias (Fumenip), AC.

References


II Manuscript received September 20, 2011; accepted for publication, December 2, 2011.

Saul Oswaldo Lugo Reyes
Immunodeficiencies Research Unit, National Institute of Pediatrics, 1 IMAN Ave, Insurgentes Cuicuilco, Coyoacan Mexico City, DF 04530, Mexico
E-mail: dr.lugo.reyes@gmail.com

© 2012 Esmon Publicidad
Skin Reactions to Gadolinium-Based Contrast Media

M Tomás, V Fuentes Aparicio, I. Zapatero Remon, E Alonso Lebrero, S Infante Herrero
Allergy Service, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Key words: Gadolinium-based contrast media. Drug allergy. Immunologic Tests. Magnetic resonance imaging. Hypersensitivity reactions.


Gadolinium-based contrast media are used for magnetic resonance imaging (MRI). The most common agents are gadopentetate dimeglumine (Magnevist), gadobutrol (Gadovist), gadobenate dimeglumine (MultiHance), gadoxetate disodium (Primovist), and gadoteridol (Prohance).

Adverse reactions are uncommon, with prevalence ranging between 0.066% and 1.47%. The most common types of adverse reactions are hypersensitivity reactions, such as erythema and urticaria; anaphylaxis occurs in just 0.01% of cases.

We report 2 cases of hypersensitivity to gadolinium-based contrast agents, including that of a patient in whom positive skin test results suggest a possible immunoglobulin (Ig) E-mediated mechanism.

The first case involved a 17-year-old black girl with a history of albinism, hypothyroidism, and cervical squamous cell carcinoma treated with surgery. She required 6-monthly MRI for monitoring of her tumor. In July 2009, she developed generalized urticaria and pruritus immediately after MRI with gadoteridol. She was treated with antihistamines and corticosteroids, and her condition improved in 2 to 3 hours. She had tolerated the same procedure with the same contrast agent implicated in the reaction, because it had been withdrawn from the hospital.

The second case involved a 4-year-old North African girl with a history of low-grade chiasmatic-hypothalamic glioma that had been treated with chemotherapy. She also required 6-monthly MRI to monitor her glioma. In July 2010 she developed a generalized rash with no other symptoms immediately after MRI with gadobenate dimeglumine. She resolved in minutes with antihistamines. She had previously tolerated MRI with gadopentetate dimeglumine.

Skin prick tests (SPT, 1:1) and intradermal tests (IDT, 1:10) were performed with the agents implicated in the reactions and several alternatives: gadopentetate dimeglumine, gadobutrol, gadobenate dimeglumine, gadoteridol, and gadoxetate disodium.

SPT was performed first. When the results were negative, IDT was performed with contrast agents from the same series. Histamine and normal saline were used as positive and negative controls, respectively, and a wheal of greater than 3 mm was considered positive. The tests were also performed in a group of 10 nonatopic individuals and an atopic control group, with negative results in all cases.

Challenge testing was performed, following signed informed consent from the parents, with the injection of an alternative gadolinium contrast (single dose according to the patient’s weight) diluted in 250 cc of saline.

In case 1, the SPT and IDT results were negative for all the gadolinium-based contrast media tested. As the patient needed to continue monitoring with MRI, we performed a controlled exposure test with gadoteridol, with negative results. We did not test gadopentetate dimeglumine, the agent that had been implicated in the reaction, because it had been withdrawn from the hospital.

In case 2, the SPT results were negative for all the agents tested. The IDT results (with immediate reading) were negative for gadopentetate dimeglumine and gadobenate dimeglumine and positive for gadoteridol, gadobutrol, and gadoxetate disodium (Figure). For the challenge test, we used gadobenate dimeglumine, which had yielded negative SPT and IDT results.

The girl tolerated the contrast without problems.

Hypersensitivity reactions with gadolinium-based contrast agents are rare, with very few cases described in the literature. The first case dates from 1995, when Jordan et al [1] reported anaphylactic shock to gadopentetate dimeglumine. The next case was reported in 2005 by Rahman et al [2], who described a case of anaphylaxis following initial exposure to a gadolinium-based contrast. Kalogeromitros et al [3] described a similar case after MRI with gadobenate dimeglumine, which produced a positive IDT response. Hasdenteufel et al [4] reported 2 cases of anaphylactic shock after initial exposure to gadopentetate dimeglumine in MRI. In both cases, the SPT and IDT results were positive for the agent involved. In 2009, Watson et al [5] described the case of a 58-year-old woman who developed anaphylactic shock after exposure to a gadolinium-based contrast agent, but an allergy study was not performed because of the poor baseline condition of the patient. Finally, Galera et al [6] described 2 cases of anaphylaxis after the administration of gadoteridol and gabodenamine dimeglumine. In both cases, the skin tests were performed with the contrast involved in the reaction and a series of alternatives. The patient exposed to gabodenamine dimeglumine had a positive IDT to this agent, while the other patient had a positive SPT to gadoteridol (the agent implicated in the reaction) and a positive IDT to the other agents tested. The positive skin test results suggest that dilutions do not cause a reaction and indicate the possibility of a delayed-type hypersensitivity reaction.
of multiple sensitization, highlighting the need for assessing cross-reactivity between contrast agents.

None of the cases published to date have suggested an alternative for patients who need to undergo gadolinium MRI in the future. In our first case, the skin tests were negative but the suggestive clinical reaction and the need for the patient to continue MRI monitoring led us to perform a challenge test with an alternative agent. In the second case, the positive IDT results may indicate an IgE-mediated mechanism. As the skin test results were positive for several gadolinium-based contrasts, we considered the possibility of an alternative radiological method, but this was not possible because MRI was necessary to monitor the patient’s disease. We therefore performed a challenge with gadobenic acid as this had produced a negative IDT response. This contrast agent is used to display liver structures, although it can be used for cranial structures in the first phase of intravenous infusion. The patient tolerated the agent well.

Our findings for this second case are consistent with those described by Galera et al [6] and we consider that a positive skin test result for several gadolinium-based contrast agents might suggest cross-reactivity. We emphasize the importance of challenge testing with alternative contrasts, where possible, as this may be of vital importance for patients who require radiological monitoring. Further studies are necessary to elucidate the mechanisms potentially involved in these reactions.

References


Margarita Tomás
Servicio de Alergología
Hospital General Universitario Gregorio Marañón
Doctor Esquerdo, 46
28007 Madrid, Spain
E-mail: margui.tomas@gmail.com

Occupational Asthma Due to Western Red Cedar in a Guitar Maker

P Barranco, S Olalde, M Caminoa, I Bobolea, T Caballero, V del Pozo, S Quirce
1 Department of Allergy, Hospital La Paz, Health Research Institute (IdiPAZ), Madrid, Spain
2 CIBER de Enfermedades Respiratorias CIBERES, Madrid, Spain
3 Department of Immunology, Fundación Jiménez Díaz, Madrid, Spain
4 Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER)- U754, Madrid, Spain

Keywords: Guitar maker, Occupational asthma, Western red cedar.

Palabras clave: Guitarro, Asma ocupacional, Madera de cedro rojo del Canadá

Occupational asthma caused by exposure to western red cedar (WRC) (Thuja plicata) has been described in the sawmill industries of the Pacific Northwest [1] but no cases have been reported to date in Europe. One of the nonvolatile compounds isolated from WRC, plicatic acid, has been identified as the agent responsible for asthma due to WRC [2].

WRC is used in the manufacture of guitars due to its elasticity and tone. Although this wood was introduced to the Spanish guitar industry in the 1970s, no cases of occupational asthma among guitar makers have been reported to date.

We report the case of a 22-year-old male smoker who had worked making hand-crafted guitars since 2006; his job involved sanding and shaping wood, especially WRC. In September 2009 he developed a respiratory infection followed by dry cough, dyspnea, and wheezing. Despite treatment with salmeterol/fluticasone (50/500 μg twice daily) the dyspnea persisted, predominantly at night. He experienced a marked improvement at weekends but his symptoms worsened on Monday nights. His condition worsened progressively for 3 months and he required treatment for severe dyspnea and cough in the emergency department on 3 occasions.

A chest radiograph and blood tests were normal except for eosinophilia (850 eosinophils/mm³). Spirometric parameters were within normal limits, with a forced vital capacity (FVC) of 5.19 L (103% of predicted), a forced expiratory volume in the first second of FEV₁ of 4.10 L (96%), and an FEV₁/FVC ratio of 75.3%. The bronchodilator test was negative. The methacholine inhalation test was positive (20% fall in FEV₁ from baseline [PC20] at 1 mg/mL) and the fraction of exhaled nitric oxide (FeNO) was 42 ppb. On evaluating the patient after he had been absent from work for 15 days, the methacholine test was negative (PC₂₀ > 16 mg/mL) and FeNO was 30 ppb. Total serum immunoglobulin (Ig) E was 146 kU/L.

Skin prick tests with common Aeroallergens and commercial wood extracts (Bial-Aristegui, ) were negative, as was a prick test with a sawdust extract of WRC (10% wt/vol). An extract of WRC free of volatile components was prepared [3] at 2.5 mg/mL.
Figure. Specific inhalation challenge with western red cedar at 2.5 mg/mL in the patient and in a control. SaO2 indicates oxygen saturation by pulse oximetry; FeNO, exhaled nitric oxide; FEV1, forced expiratory volume in the first second; PEF, peak expiratory flow.

A prick test with this extract was negative in the patient and in 5 nonexposed controls.

After the patient had stopped working for 4 weeks and was free of symptoms, we performed a specific inhalation challenge (SIC) [3] with WRC at 2.5 mg/mL and with a control solution using a DeVilbiss 646 nebulizer (DeVilbiss) at tidal breathing for 1 to 8 minutes. Spirometry was performed at 5, 10, 20, 30, 40, 60 and 120 minutes after the challenge. From that moment, peak expiratory flow (PEF) and FEV1, measurements were performed hourly with an electronic PEF/FEV1 meter (Vitalograph) for 24 hours, except during sleep. The SIC elicited an isolated late asthmatic response, with a maximum fall in FEV1 of 40% 10 hours after the challenge. An increase in peripheral blood eosinophils and a decrease in oxygen saturation were observed 24 hours after the SIC, but no significant changes were observed in FeNO (Figure). The methacholine inhalation test could not be repeated 24 hours after the SIC because the patient still had airflow obstruction and required treatment with inhaled bronchodilators. No reaction was observed in a healthy nonexposed control.

A basophil activation test (Basotest) was performed with WRC extract at different concentrations (0.625, 1.25, 2.5 and 5 mg/mL) using whole blood obtained from the patient and a control [4]. A 2-fold increase in WRC-induced degranulation was observed in the patient compared to the control with WRC 5 mg/mL.

The patient was diagnosed with occupational asthma due to WRC. He quit his job and had no further exposure to WRC. Six months later he was asymptomatic.

The pathogenesis of occupational asthma due to WRC remains to be elucidated. Histamine and leukotrienes can be detected in bronchoalveolar lavage fluid after inhalation of plicatic acid. Peripheral blood basophils from patients with WRC-induced asthma release histamine with plicatic acid, but specific immunoglobulin (Ig) E to this compound is detected only in a small proportion of patients [5]. Because our patient had a late asthmatic response with peripheral blood eosinophilia (probably due to eosinophilic airway inflammation) and a positive basophil activation test after a challenge with WRC, we can assume the involvement of an immunologic mechanism.

References


*Manuscript received October 4, 2011; accepted for publication, December 15, 2011.*

**Pilar Barranco**
Departamento de Alergia
Hospital Universitario La Paz
P. Castellana, 261
28046 Madrid (Spain)
E-mail: pbarranco.hulp@salud.madrid.org
Frey Syndrome in Children: A Nonallergic Cause of Facial Erythema Triggered By Food

C Ortega Casanueva, S Sánchez-García, P Rodríguez del Río, C Escudero, V Andregnette, MD Ibáñez
Department of Allergology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain


Food allergy is frequently overdiagnosed, particularly in individuals who develop a rash immediately after ingestion. This may lead to unnecessary tests and delayed diagnosis.

Frey syndrome, otherwise known as auriculotemporal syndrome or gustatory flushing, is relatively common in adults following nerve injury in parotid surgery but it has also been reported in children. It is relatively unknown among primary care providers and is usually confused with an underlying food allergy. We report a series of cases of Frey syndrome in children and emphasize several aspects that should lead any medical practitioner to reject a diagnosis of food allergy.

Nine children referred to our outpatient clinic in the last 10 years presented linear flushing in the auriculotemporal region that normally appeared during the intake of solid or acidic foods. The studies to exclude food allergy consisted of a complete description of clinical symptoms, skin tests (prick and/or prick to prick) and/or oral challenges with the implicated foods.

The children, 6 boys and 3 girls, were aged between 5 months and 7 years. Only 1 of them had a previous diagnosis of atopic disease (dermatitis, asthma, or food allergy). Gestational age at birth was at least 38 weeks, but delivery in all cases had been complicated by failure to progress and required the use of forceps. When injured, the nerve undergoes abnormal regeneration. The aberrant parasympathetic nerves fibers are stimulated during the chewing of diverse foods, resulting in pathological vasodilation rather than salivation [2].

In the case of adults, recent publications have reported the onset of this disorder in patients who have undergone parotid surgery [3,4]; the disorder commonly appears within 1 month to 5 years of surgery and affects 37% to 100% of such patients [5].

Frey syndrome is relatively uncommon in children and is usually related to perinatal birth trauma [6], although congenital nerve injury has also been postulated as a potential cause [7]. There have also been recent reports of an association with facial plexiform neurofibromas [8] and congenital hemangiopericytoma [9].

All of the 9 children in our series had been delivered with the assistance of forceps and none of them had a relevant history of infection, surgery, or accidental trauma. Only 1 of the 9 children had clinical hyperhidrosis. While this is the predominant symptom in adults, it is unusual in children. A diagnosis of food allergy was initially considered by the pediatrician in all of the cases reported, with lengthy investigations, causing anxiety among some parents, before Frey syndrome was diagnosed.

Although a diagnosis of Frey syndrome can be based exclusively on reported symptoms, it is usually diagnosed several months and sometimes even several years after the onset of symptoms [10]. It is noteworthy that in our series, none of the children had been avoiding certain foods for more than 4 years because they had not been diagnosed correctly. Misdiagnosis can generate considerable costs and unnecessary tests and elimination diets, all of which can be easily avoided by increasing awareness of this syndrome.

Several aspects should be considered by physicians to discard food allergy; these include the presence of unilateral flushing always in the same location, the absence of other symptoms (eg, pruritus, vomiting, diarrhea), rapid resolution, and the diversity of foods—mostly acidic—that cause symptoms.

Frey syndrome in children is self-limiting, benign, and does not require treatment. Familiarity with this condition among allergists and pediatricians should help to reduce the misinterpretation of this relatively rare condition as a food allergy.
<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past history</td>
<td>Obstetrical</td>
<td>Egg and cow’s</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>brachial plexus</td>
<td>milk allergy</td>
<td>lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset, mo</td>
<td>12</td>
<td>34</td>
<td>5</td>
<td>18</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Age at diagnosis, mo/y</td>
<td>20 mo</td>
<td>7 y</td>
<td>6 mo</td>
<td>24 mo</td>
<td>7 mo</td>
<td>14 mo</td>
<td>5 y</td>
<td>5 mo</td>
<td>3 y</td>
</tr>
<tr>
<td>Food involved</td>
<td>Egg</td>
<td>Candies</td>
<td>Apple</td>
<td>Bread</td>
<td>Apple</td>
<td>Orange</td>
<td>Kiwi</td>
<td>Apple</td>
<td>Candies</td>
</tr>
<tr>
<td></td>
<td>Chicken</td>
<td>Fries</td>
<td>Orange</td>
<td>Egg</td>
<td>Banana</td>
<td>Cookies</td>
<td>Watermelon</td>
<td>Pork</td>
<td>Pear</td>
</tr>
<tr>
<td></td>
<td>Pork</td>
<td>Banana</td>
<td>Kiwi</td>
<td>Candies</td>
<td></td>
<td></td>
<td>Strawberry</td>
<td>Hake</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hake</td>
<td>Burger</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Erythema on the right cheek</td>
<td>Erythema on the right cheek</td>
<td>Erythema on the left cheek</td>
<td>Erythema and sweating on the left cheek</td>
<td>Erythema on the left cheek</td>
<td>Erythema on the left cheek</td>
<td>Erythema on the right cheek</td>
<td>Erythema on both cheeks</td>
<td>Erythema on the right cheek</td>
</tr>
<tr>
<td>Oral food challenge</td>
<td>ND</td>
<td>Candies</td>
<td>ND</td>
<td>Bread</td>
<td>Banana</td>
<td>ND</td>
<td>Fries</td>
<td>Candies</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: ND, not done; NR, not relevant.
References


Anaphylaxis Due to Orange Soft Drinks

LA Navarro,1 C Pastor-Vargas,2 JJ Liñana,1 I Martínez,3 AS Muroto,2 F Vivanco,2 B Bartolomé1
1 Allergy Unit. Hospital Lluís Alcanyís Xàtiva, Spain
2 Instituto de Investigación Sanitaria-Fundación Jiménez Díaz, Madrid, Spain
3 Department of Internal Medicine. Hospital Lluís Alcanyís Xàtiva, Spain

Key words: Orange. Soft drinks. Anaphylaxis. Cit s 1.


Citrus sinensis is a tree that belongs to the Rutaceae family; its fruit, the sweet orange, is widely consumed throughout Europe. Valencia, which is the largest producer of sweet oranges in Spain, is one of the most important orange-growing areas in the world. Spain alone produced 5.7 million tons of this fruit in 2011. Sweet orange is not considered to be a common allergenic fruit, although 3 allergens have been described to date: Cit s 1 (germin-like protein), Cit s 2 (proflin), and Cit s 3 (nonspecific lipid transfer protein) [1,2]; this last allergen has been found to show cross-reactivity with the major peach allergen Pru p 3 [3]. However, no cases of allergy to orange soft drinks have been reported in the literature.

We report the case of a 23-year-old woman who experienced an episode of anaphylaxis 10 minutes after handling sweet oranges in a fruit warehouse (an orange storage network), where she had been working for a month. Because of this episode, she left the job and some months later experienced contact urticaria when squeezing an orange; she also experienced oral allergy syndrome after drinking several orange soft drinks (Sunny Delight and TriNa orange) that she had previously tolerated.

Surprisingly, despite living in Valencia, she had not eaten sweet oranges for 15 years as she did not like them. She denied having clinically allergic rhinitis or asthma and tolerated various types of fruits, including citric fruit such as lemon, which she tolerated in ice cream and juice form before and after the allergic episodes described above.

Skin prick tests (SPTs) were negative for mites, fungi, and pollen (Parietaria judaica, Olea europaea, Gramineae family, Cupressus arizonica, Platanus acerifolia, and Artemisia vulgaris) and a prick test with proflin from Gramineae pollen was also negative. Extracts from sweet orange pulp and peel were prepared as follows. The pulp and peel were ground into small pieces, defatted, and extracted by magnetic stirring in 50 mM of phosphate-buffered saline (PBS) at pH 7.5 for 3 hours at room temperature. The samples were centrifuged at 5600×g for 30 minutes, and the supernatants dialyzed against water and freeze-dried. The orange soft drink extracts (Sunny Delight and TriNa) were prepared by dilution in phosphate buffer (1:2), followed by magnetic stirring for 15 minutes at room temperature, dialysis, and freeze-drying. Positive SPT
Figure. I) Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) immunoblotting results under reducing conditions. A: orange peel extract; B: orange pulp extract; C: Sunny Delight soft drink extract; D: TriNa soft drink extract; E: KAS soft drink extract. Lane P: patient serum (dilution 1:1); lane C: control serum (pool of sera from nonatopic individuals); lane M: molecular mass markers. II) SDS-PAGE immunoblotting-inhibition results with Sunny Delight extract in solid phase. Lane C: control serum (pool of sera from nonatopic individuals); lane 1: patient serum previously incubated with Sunny Delight extract; lane 2: patient serum previously incubated with orange pulp extract; lane 3: patient serum previously incubated with TriNa extract; lane 4: patient serum previously incubated with KAS extract; lane 5: patient serum previously incubated with lamb extract; lane M: molecular mass markers.

results were obtained for the pulp extract (4 × 4 mm) and the peel extract (44 × 5 mm); the results for similar tests with lemon pulp and peel extracts (all at 10 mg/mL) were all negative. The SPTs with the soft drink extracts were negative but the corresponding intradermal tests were positive in both cases (>64 × 6 mm). Furthermore, 1 hour after the intradermal test with orange extract (pulp and peel), the patient developed facial edema, dyspnea, and wheezing that required urgent medical attention.

Total serum immunoglobulin (Ig) E (UniCAP, Phadia) was 6.7 IU/mL and serum specific IgE by means of an enzyme allergosorbent test against orange peel and pulp extracts was <0.35 kU/L (class 0).

Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) immunoblotting was performed with sweet orange pulp extract. IgE immunoblotting with the patient’s serum revealed IgE-binding bands of approximately 75 kDa, 66 kDa, 57 kDa, 28 kDa, 22 kDa, and 18 kDa. The immunoblotting profile of 3 orange soft drink extracts (Sunny Delight, TriNa, and KAS) showed a strong band of 28 kDa. SDS-PAGE immunoblotting-inhibition assays showed the capacity of the orange pulp extract to inhibit the IgE binding to the Sunny Delight extract; partial inhibition was observed with the extracts from the 3 orange refreshments (Figure). This difference in IgE binding–inhibition activity must be due to the higher concentration of Cit s 1 in the orange pulp sample than in the soft drink samples.

The 28-kDa IgE binding protein was identified by MALDI-TOF (matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry) and LC-ESI-MS/MS (liquid chromatography electrospray ionization tandem mass spectrometry), and by searching the NCBI non-redundant protein sequence database using the Mascot program (http://www.matrixscience.com), as previously described [4]. The resulting peptides analyzed by MS or MS/MS corresponded to Cit s 1.

To clarify the implication of this allergen, we suggested performing an oral provocation test with orange, but this was rejected by the patient due to the symptoms she had developed after the intradermal test.

Ahrazem et al [3] showed a high frequency of Cit s 1 sensitization in individuals who did not develop symptoms on consuming oranges; this was attributed to the monovalent nature of this protein based on its N-glycan epitope. For this reason, Cit s 1 has been labeled an “equivocal allergen” [5]. We have presented an interesting case of a nonatopic patient who showed clinically relevant monosensitized allergy to Cit s 1, a sweet orange allergen, which appeared as an active allergenic component in orange soft drinks. Our findings are consistent with the IgE reactivity exhibited by Cit s 1 in heat-processed orange juice described by Crespo et al [1]. To conclude, we believe that the clinical relevance of Cit s 1 should be studied more carefully, with an independent investigation of each case.

Acknowledgments

This study was supported by a grant (RD07/006/0023) from RETIC RIRAAF (Red de Investigación de Reacciones Adversas a Alérgenos y Fármacos).
References


Nasal Challenge Test in the Diagnosis of Latex-Related Systemic Reactions

R Muñoz-Cano, 1 M Pascal, 2 M Lombardero, 3 J Sánchez-López, 1 J Bartra, 1 R Vilella, 2 C Picado, 1 A Valero 1
1Allergy Unit, Pneumology Department, ICT, Hospital Clínic-IDIBAPS, Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERESP), Universidad de Barcelona, Barcelona, Spain
2Department of Immunology, Centre de Diagnòstic Biomèdic (CDB), Hospital Clínic, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
3R&D Department ALK-Abelló S.A., Madrid, Spain

Key words: Anaphylaxis. Nasal challenge test. Natural rubber latex.

Palabras clave: Anafilaxia. Prueba de provocación nasal. Látex.

Natural rubber latex (NRL) allergy is recognized as a major health problem. Around 12% of allergic reactions occurring during anesthesia are caused by latex [1], although the incidence of latex allergy seems to have decreased in recent years [2]. None of the available diagnostic tests has 100% sensitivity.

We report the case of a 30-year-old woman who experienced anaphylactic shock during a myomectomy under general anesthesia (serum tryptase, 18.6 ng/mL at 1 hour after the reaction). The patient had a personal history of mild rhinitis and house dust mite sensitization, but neither drug-related nor food-related allergic reactions had been reported. She worked as a dental assistant and had never experienced problems with NRL gloves or occupational respiratory symptoms.

In vivo study:
The results of skin prick tests (SPT) and intradermal tests with the drugs used during anesthesia (propofol, fentanyl, midazolam, cisatracurium, and cefminox) were all negative. We performed an intramuscular challenge test with cefminox, although no allergic reaction was observed. SPT using commercial latex extract (100 IR/mL, Stallergènes) was not conclusive (wheal 3/1150 mm without erythema). Therefore, to confirm the suspected NRL allergy, we performed a prick-by-prick test with a latex glove, a rubbing test, and a glove use test, although the results were negative in all cases. In order to rule out a possible lack of efficacy of the first commercial latex extract, SPT was repeated using another commercial extract with a known latex protein concentration of 0.5 mg/mL (ALK-Abelló). We tested several dilutions (1/100 weight/volume [w/v], 1/10 w/v, and 1/1 w/v), although only the undiluted SPT (0.5 mg/mL) was slightly positive, with a wheal of 4 x 4 mm (histamine, 9 x 8 mm). We mimicked mucosal allergen exposure by performing a nasal challenge test (NCT) with the NRL extract used in the second SPT. The challenge was performed according to guidelines [3] and monitored using acoustic rhinometry. Although SPT had only been positive at 1/1 w/v, NCT was performed at 2 different concentrations (0.5 mg/mL and 0.05 mg/mL). The result was positive (decrease of >25% in nasal volume between 0 and 7 cm) only at 0.5 mg/mL. No systemic reactions were observed. A healthy control was also tested after providing written informed consent, with negative results. A thorough investigation into food sensitization related to NRL allergy (banana, kiwi, avocado, and chestnut) was negative (both history and SPT).

In vitro study: Specific immunoglobulin (Ig) E to NRL
was 0.33 kU/L (specific IgE level >0.35 kU/L was considered positive) and negligible to banana, kiwi, avocado, and chestnut extracts (ImmunoCAP, Phadia). Baseline tryptase was 4.02 ng/mL (ImmunoCAP). The patient’s serum was also tested against 103 allergenic components in a commercially available microarray (ImmunoCAP ISAC, Phadia) including the major allergenic components of latex (Hev b 1, Hev b 3, Hev b 5, and Hev b 6) and the cross-reactivity marker (Hev b 8). Specific IgE was undetectable (specific IgE >0.3 ISAC standardized units was considered positive). Given the high clinical suspicion, specific IgE determination was repeated using the Advia-Centaur IgE assay (ALK-Abelló), which showed that specific IgE for the allergenic components of latex was positive for Hev b 6 (1.75 kU/L) and negative for Hev b 1, Hev b 3, and Hev b 8. A basophil activation test was also performed on fresh whole blood using the FlowCAST kit (Bühmann), following the manufacturer’s protocol. The stimulus used was the same preparation of NRL in 0.9% saline solution (0.5 mg/mL) used for NCT, but at various dilutions in phosphate-buffered saline (1:200, 1:400, and 1:1000), as reported elsewhere [4]. All concentrations gave a positive test result for the patient (Figure) and negative result for a nonatopic control tested in parallel.

To our knowledge, this is the first report of perianesthetic latex-related anaphylaxis to be confirmed in vivo using NCT only. This test seems to be a simple, useful, and safe tool for the diagnosis of latex allergy beyond respiratory symptoms. Therefore, it should be taken into account when latex allergy is suspected and conventional diagnostic tools (SPT and serum specific IgE) are not conclusive or other in vitro tests are not available. As latex can trigger potentially severe reactions, all in vivo latex allergy tests, NCT included, should be performed in the hospital by well-trained medical staff with resuscitation facilities on hand in case of emergency.

References


Manuscript received August 30, 2011; accepted for publication January 4, 2012.

Rosa Muñoz-Cano, MD
Allergy Unit, Pneumology Department, ICT Hospital Clinic de Barcelona C/ Villarroel, 170 Esc. 6-Pl. 0 08036 Barcelona, Spain
E-mail: rmunoz@clinic.ub.es
Cow’s milk protein (CMP) allergy is one of the most common causes of food allergy in childhood. In Spain, the incidence of allergy to cow’s milk in the first year of life ranges between 0.36% and 1.9% [1,2]. Most allergic children achieve tolerance during the first 4 years of life, although the disease has been reported in children as old as 16 years [3].

Caseins are major allergens in CMP allergy, and a high degree of cross-reactivity has been demonstrated between caseins in the milk of different species of animals. Cross-reactivity results from homology between the amino acid sequences of these proteins [4]. Children who are allergic to CMPs are sensitized to whey proteins, the casein fraction, or both, and many also react to goat’s milk or sheep’s milk because of the high degree of homology between the corresponding proteins. Conversely, goat’s milk allergy does not usually involve allergic cross-reactivity to cow’s milk. The allergens responsible are mainly caseins and calcium-binding proteins, such as αs1-casein, αs2-casein, and β-casein, but not whey proteins [5].

Treatment of CMP allergy is based on avoidance of cow’s milk and its derivatives, as well as milk and dairy products from other mammals (especially goat and sheep), because of cross-reactivity between different species. The most recent treatment option is specific oral tolerance induction (SOTI). However, it is important to note that SOTI to CMPs does not induce tolerance to milk from other mammals, as demonstrated in a recent study [6].

The aim of this study was to determine differences in the pattern of sensitization to goat’s milk proteins in goat’s milk–tolerant and cow’s milk–intolerant patients who successfully completed SOTI to cow’s milk. We report 8 children sensitized to goat’s milk with good tolerance to cow’s milk after SOTI. The sample was divided into 2 groups: group A included 4 children (aged 2 to 9 years) who were desensitized to CMP at age 2 to 6 years but who did not tolerate goat’s milk (goat’s milk immunoglobulin [Ig] E, 12.5-100 kU/L); group B included 4 children (aged 3 to 8 years) who were desensitized to CMP at age 2 to 5 years but who tolerated goat’s milk (goat’s milk IgE, 0.9-40.6 kU/L).

Skin prick tests were performed with goat’s milk (10 mg/mL) (DIATER), whole cow’s milk (10 mg/mL) (ALK-Abelló), and isolated CMPs: casein (10 mg/mL) (LETI), αs1-casein, αs2-casein, β-casein, αlactalbumin, and β-lactoglobulin (5 mg/mL, 5 mg/mL) (DIATER) following standardized methodology [7].

Serum determinations of specific IgE to goat’s milk, cow’s milk, and isolated CMPs were performed using CAP-FEIA (Phadia). Sodium dodecyl sulfate polyacrylamide gel electrophoresis was carried out using cow’s milk and goat’s milk following the methodology of Towbin et al [8]. Immunoblotting inhibition was carried out with serum pools from each group incubated with serial dilutions of cow’s milk and goat’s milk (protein content of 10, 1, and 0.1 mg).

Open controlled challenge tests with goat’s milk were performed in the Allergy Unit of our hospital (Hospital General Universitario, Valencia, Spain), where appropriate medication and resuscitation equipment were available. Informed consent was previously obtained from the parents. All challenge tests were carried out under the control of an allergist. Patients in group A had multiple IgE binding bands for CMPs and goat’s milk proteins (molecular weight range compatible with casein, α-lactalbumin, and β-lactoglobulin). Sera from patients in group B recognized multiple bands for CMPs, although at low intensity and only in the range of the α-caseins and β-caseins of goat’s milk proteins. Sera from patients in group B were completely inhibited with cow’s milk. Sera from patients in group A reacted with goat’s milk proteins in the range of caseins after inhibition with cow’s milk (Figure). Cow’s milk SOTI has proven to be an effective therapeutic procedure that achieves tolerance in most CMP-allergic patients [9]. Nevertheless, some patients can present allergic reactions after ingestion of goat’s milk [6].

The cross-reaction between CMPs and goat’s milk proteins means that most patients who are allergic to cow’s milk cannot tolerate goat’s milk [10]. Conversely, goat’s milk allergy does not usually involve an allergic reaction to cow’s milk. A patient can become sensitized to specific proteins of goat’s milk without...
experiencing cross-reactions with CMPs, thus explaining why allergic patients tolerate cow’s milk, but not goat’s milk [5].

The results of this study suggest that patients who do not tolerate goat’s milk after cow’s milk SOTI are sensitized to specific goat’s milk caseins without cross-reactivity to CMPs. Cow’s milk SOTI can induce tolerance to CMPs but does not guarantee tolerance to the milk of other mammals. Once cow’s milk SOTI has been completed, a diet free of goat’s milk should be adhered to until tolerance has been tested using controlled challenge testing. We conclude that patients who are allergic to goat’s milk after cow’s milk SOTI show sensitization to goat’s milk proteins that have no cross-reactivity with CMPs, thus explaining the persistence of clinical reactivity and confirming the specificity of SOTI.

References


Aplastic anemia is a type of peripheral blood pancytopenia in which hypopcellular bone marrow (<25% cellularity) is confirmed by biopsy. The choice between the 2 possible treatment modalities—bone marrow transplantation and immunosuppression—depends on the availability of a histocompatible family donor, patient age, and severity of the aplasia. Immunosuppressive therapy includes antithymocyte globulin (ATG), ciclosporin, prednisone, and other drugs [1].

A 15-year-old girl with no history of allergy was referred to the hematology department of our hospital with thrombocytopenia that had been detected in June 2010. Blood tests revealed pancytopenia in peripheral blood. Bone marrow biopsy showed marked hypoplasia of the 3 hematopoietic series (<25%). She was finally diagnosed with idiopathic aplastic anemia. Bone marrow transplant from a histocompatible sibling was proposed, although this was not possible because the potential donor was diagnosed with mixed connective tissue disease. Therefore, immunosuppressive therapy with rabbit ATG (rATG), ciclosporin A, and prednisone was prescribed. As recommended [2], 1 hour before the infusion of rATG, the patient was premedicated with acetaminophen 1 g, methylprednisolone 75 mg, and dexchlorpheniramine maleate 5 mg.

rATG therapy was started at 25 mg/h (total scheduled infusion of 6 hours). After 90 minutes the patient developed pharyngeal itching and dyspnea. The infusion was stopped, hydrocortisone 100 mg was administered, and her condition improved within 20 minutes. Five hours later, the infusion was restarted more slowly to be administered over 12 hours; however, after 90 minutes the patient complained of pharyngeal itching, dyspnea, chest tightness, wheezing, and generalized hives. Her condition improved after administration of intravenous hydrocortisone.

Treatment with rATG was discontinued, and the drug allergy unit of our department was consulted to assess desensitization to rATG.

Skin tests were performed following the recommendations of the European Academy of Allergy and Clinical Immunology [3]. Prick testing was performed with a commercial extract of rabbit epithelium (ALK-Abelló). Serum tryptase and total and specific immunoglobulin (Ig) E were determined using ImmunoCAP (Phadia). Prick testing with undiluted rATG at 5 mg/mL (Genzyme Corporation) and intradermal testing with 0.05 mL diluted in saline from 1:100 000 to 1:100 were performed. Skin testing...
was not performed in healthy controls for ethical reasons (risk of sensitization to rATG). After obtaining informed consent, we applied a previously described protocol for rapid intravenous desensitization to chemotherapy and monoclonal antibodies. We modified the protocol in order to finish in 24 hours instead of the previously described 5.8 hours [4]. Three solutions of rATG (1.5, 15, and 150 mg) in saline (250 mL) were delivered in 12 consecutive steps at increasing rates every 15 minutes. From step 12, the infusion rate remained unchanged over 24 hours for 5 days (150 mg/d). Dexchlorpheniramine maleate 5 mg and methylprednisolone 75 mg were administered intravenously every 12 hours.

The results of prick testing with rabbit epithelium and undiluted rATG and specific IgE to rabbit epithelium and meat were negative. Levels of total IgE and serum tryptase were 134 EU/mL and 4.02 μg/L, respectively. Intradermal testing with rATG revealed an increase in the largest diameter of the wheal at 20 minutes, although this was similar at all dilutions (1/100 000 to 1/100).

Drug desensitization was completed successfully, and the patient received rATG for 5 days. The Table summarizes the incidents recorded during the desensitization protocol.

Until 2005, both equine ATG (eATG) and rATG were available. However, the only available preparation since then has been rATG, which is a purified immunoglobulin prepared from hyperimmune serum of rabbits immunized with human thymic lymphocytes. The result is a product rich in antihuman T-cell antibodies, which bind to the surface of circulating T cells and T cells within lymphoid organs, thus reducing the number of functional T lymphocytes and creating an immunosuppressive effect [2,5].

Anaphylaxis has been reported after administration of eATG and rATG [2,5]. Because of the potential for serious allergic reactions, the manufacturer of eATG recommended skin testing prior to treatment, although the predictive value of this approach has not been proven clinically [5]. In contrast, skin testing is not recommended before administering rATG, because it is a poor predictor of anaphylactic reactions [5]. Desensitization protocols have been developed and are used in patients with allergic reactions to various drugs [4].

A search in PubMed revealed only 5 cases of desensitization, all of which were to eATG, but none to rATG. Hall and Hagemann [6] reported a case of successful desensitization to eATG and reviewed 4 previously published cases [7-9], 2 of which had an unsuccessful outcome [9]. Most of these authors [6-9] suspected an IgE-mediated reaction and based their diagnosis on skin testing; however, false-positive results have been recorded with intradermal testing [8].

Although we found intradermal tests to be positive in the immediate reading, we cannot state that the mechanism is IgE-mediated, since no progressive enlargement of the wheal was observed with increasing concentrations of the drug. In addition, a latency period exceeding 1 hour and no prior exposure to rATG rule this mechanism out, and tests would have to be performed on controls to exclude an irritant effect. We suggest other possible mechanisms. Lysis of T lymphocytes is dependent on complement activation [2]; therefore, it is likely that the complement fragment C5a (anaphylatoxin) had a role in the reaction our patient experienced. Moreover, the action of rATG targets multiple CD molecules located on the membrane of T lymphocytes, but which are not exclusive to these cells: some CD molecules are also present in monocytes, basophils, and mast cells [10], with the result that activation of these cells with the subsequent release of their mediators is probable. Finally, lysis of T lymphocytes and monocytes and subsequent release of their cytokines and chemokines, respectively, all of which can act on basophils releasing histamine (histamine-releasing factors), could also explain such a reaction. These complex immunological mechanisms, whether alone or in combination, seem to be a likely explanation for the reaction. Our findings are consistent with those of previously reported reactions to eATG [6-9], namely, symptoms, doubtful interpretation of skin test results, and adverse events that respond to antihistamines during desensitization. These findings strengthen our hypothesis that this type of reaction could be associated with the mechanism of action, which is the same.

Table. Incidents During Desensitization to Rabbit Antithymocyte Globulin

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 AM Start of infusion</td>
<td>12:10 PM Extensive erythema with severe itching</td>
<td>8:00 AM Slightly pruriginous erythema on trunk, arms, and neck</td>
<td>Mild nonpruritic erythema</td>
<td>No symptoms</td>
</tr>
<tr>
<td>2:00 PM Mild nonpruritic erythema on trunk (15 minutes’ duration)</td>
<td>3:00 PM itching on scalp and arms with erythema on neck and arms that lasted 1 hour; chest tightness without dyspnea or wheezing (1 hour’s duration)</td>
<td>1 episode of vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7:00 PM</td>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9:00 PM</td>
<td>Erythema on legs that lasted 1 hour</td>
<td>No treatment</td>
<td>Prescription of oral dexchlorpheniramine maleate 6 mg at midday</td>
<td>No treatment</td>
</tr>
</tbody>
</table>

Normal vital signs | Normal vital signs | Normal vital signs | Normal vital signs | Normal vital signs |

No treatment | Intravenous dexchlorpheniramine maleate 5 mg | Prescription of oral dexchlorpheniramine maleate 6 mg at midday | No treatment | No treatment |
in both types of ATG, and not with the antigenic characteristics, which are obviously different.

More studies are necessary to clarify the immunological mechanisms involved in these reactions, the most appropriate diagnostic method, and the changes that occur during the desensitization process.

Data from this report were included in a poster presentation at the 30th Congress of the European Academy of Allergy and Clinical Immunology, 11–15 June, Istanbul, Turkey.

References


**Practitioner’s Corner**

Delayed-Type Hypersensitivity to Fenofibrate

V Pecora, E Nucera, A Aruanno, A Buonomo, D Schiavino

Allergy Department, Catholic University - Policlinico “A. Gemelli”, Rome, Italy

Key words: Lipid-lowering drugs. Fibrates. Cell-mediated drug allergy. Cross-reactivity.

Palabras clave: Medicación hipolipemiante. Fibratos. Alergia a medicamentos mediada por células. Reactividad cruzada.

Statins and fibrates are the 2 most commonly used types of lipid-lowering drugs for the prevention of cardiovascular disease [1]. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase by reducing endogenous cholesterol synthesis, while fibrates promote catabolism of very-low-density lipoprotein (VLDL) in bile by reducing synthesis of VLDL and blocking HMG-CoA reductase [2]. Statins and fibrates are generally well tolerated. Their side effects are infrequent and include myalgia with consequent increased creatine phosphokinase [3-5] and hepatotoxicity associated with changes in transaminase levels [6-7]. No allergic reactions to these medications have been described.

We report the case of a 77-year-old woman with dyslipidemia who did not tolerate long-term administration of fluvastatin, which was suspended after she experienced myalgia and elevated liver enzyme levels (aspartate and alanine aminotransferase). An alternative lipid-lowering drug, fenofibrate, was prescribed at the normal adult dose (200 mg/d) to control cardiovascular risk. She experienced generalized maculopapular rash immediately after taking the tenth tablet and was treated in the emergency room with oral corticosteroids, whose dose was gradually tapered at home.

The patient was referred to our allergy unit. Her clinical history was negative for other allergic diseases. An allergy workup was performed (skin prick test and patch test with fenofibrate), and an oral challenge test with alternative lipid-lowering agents was planned.

Skin testing was conducted using undiluted solution of the commercial drug obtained from the tablet powder diluted with a drop of saline, as recommended by the European Network on Drug Allergy (ENDA) [8]. We tested the fenofibrate solution on the volar surface of the forearm using the prick method and read the reaction at 20 minutes. A positive control (histamine, 10 mg/mL) and a negative control (0.9% saline) were also used.

Patch testing was performed by applying the undiluted solution in the interscapular region and the reaction was read at 72 hours. An uncoated polyester patch that did not contain any allergen or vehicle was used as a negative control. Positivity was assessed according to the recommendations of the ENDA [8].

We also performed both tests in 5 healthy adults. The immediate reading of the skin test was negative. The response to the patch test was positive (72 hours), with erythema, wheals, and vesicles at the skin site tested with fenofibrate. The results of the tests in the 5 healthy adults were negative.

The clinical history and the positive patch test results indicated a diagnosis of delayed-type hypersensitivity to fenofibrate.

Considering that the patient needed to use lipid-lowering agents to reduce the risk of heart disease and stroke, we performed oral challenge tests with an ion-exchange resin (cholestyramine) and a dietary supplement (policosanol, red yeast, berberine, and a drop of saline, as recommended by the European Network on Drug Allergy Practice. 5th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2008. chap 29. p. 359-383

Pedro Bobadilla-González, MD, PhD

Allergy Department

Infanta Cristina University Hospital

Avda de Elvas, s/n

06080 Badajoz, Spain

E-mail: pbg3236@gmail.com

Manuscript received October 16, 2011; accepted for publication January 4, 2012.
Based on the negative results of the skin prick test and patch test, the patient underwent a single-blind oral challenge test with gemfibrozil (up to 600 mg). As the patient tolerated this fibrate well, she was prescribed the recommended daily dose (600 mg twice a day 30 minutes before the morning and evening meals).

The clinical features and timing of the adverse reaction presented by our patient were highly suggestive of a cell-mediated reaction, although delayed-type reactions to fibrates have not been reported in the medical literature. Patch testing is a useful tool for evaluating nonimmediate reactions to systemic drugs [9].

We show how fibrates, which are generally regarded as safe and well tolerated, can induce an allergic reaction. Our findings are consistent with a diagnosis of cell-mediated allergy to fenofibrate and possible cross-reactivity to bezafibrate.

The changes made in the molecular structure of fenofibrate and bezafibrate to enhance target specificity and therapeutic activity could reasonably explain the lack of cross-reactivity between these fibrates and gemfibrozil. The literature contains no data on the tolerability of gemfibrozil in patients with a delayed-type hypersensitivity reaction to fibrates.

Based on our experience, gemfibrozil could be a safe alternative to fenofibrate. Our findings should be confirmed by further studies with this drug.

References


Manuscript received October 20, 2011; accepted for publication January 9, 2012.

Domenico Schiavino, MD
Allergy Department, Catholic University
Policlinico “A. Gemelli”
Largo F. Vito, 1
00168 Rome, Italy
E-mail: allergologia@hotmail.com
A Sea Urchin Roe Tropomyosin-Like Protein Is Recognized in Vitro by Shrimp-Allergic Individuals

M Pascal,1,2 G Grishina,1 A Yang,3 R Ayuso1
1 Division of Allergy & Immunology and The Jaffe Food Allergy Research Institute, Mount Sinai School of Medicine, New York, NY, USA
2 Department of Immunology, Allergy Unit, Centre de Diagnòstic Biomèdic (CDB), Hospital Clínic, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) Barcelona, Spain
3 Division of Clinical Immunology and Allergy, University of São Paulo School of Medicine, São Paulo, Brazil

Key words: Sea urchin roe. Allergy. Tropomyosin.
Palabras clave: Erizo de mar. Alergia. Tropomiosina.

Shrimp is the most common cause of shellfish allergy. Several allergens have been described, the most allergenic of which is tropomyosin, which in addition is responsible for immunoglobulin (Ig) E cross-reactivity with crustaceans, other arthropods, and mollusks [1]. The safe ingestion of other marine invertebrates by crustacean-allergic patients has not been described, and the general recommendation is to avoid all shellfish, including sea urchins [2]. Sea urchins are marine invertebrates belonging to the phylum echinoderms. They are considered seafood, despite the fact that they are not related to fin fish, mollusks, or crustaceans. Their reproductive organs (roe) are used either raw or briefly cooked in Korean and Japanese cuisine (they are called uni in sushi) throughout the world. They are considered a delicacy and are becoming increasingly popular. Although delayed hypersensitivity skin reactions due to stings have been reported [3], immediate hypersensitivity is rare [4-6]. Recently the major allergen of sea urchin roe was identified as a major yolk protein (160 kDa) [7].

This study aimed to address whether shrimp-allergic patients recognize sea urchin allergens. Ten adult and pediatric shrimp-allergic patients with a positive double-blind, placebo-controlled food challenge with shrimp but no previous exposure to urchin roe were selected. IgE recognition of shrimp (Litopenaeus vannamei) and urchin roe extracts was evaluated as previously described [8]. Raw and boiled roe extracts were prepared from fresh green sea urchins obtained from a local store. Briefly, the roe was separated from the spiny shell and brown inards and ground. One portion was boiled in distilled water. Protein was extracted from manually homogenized raw and boiled roe by agitation in phosphate buffer saline-containing protease inhibitor cocktail without EDTA (Roche) and with 0.05% sodium azide overnight at 4°C. The mixture was centrifuged at 3000 rpm for 10 minutes and at 12600 rpm for 30 minutes at 4°C. The pellets and supernatants were analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) (Nupage 4-12% Zoom Gels; Invitrogen). The pellets showed the best protein discrimination and thus were used. Protein

Figure. A, Immunoglobulin E immunoblotting with boiled and raw shrimp extracts. B, Immunoblotting with boiled and raw sea urchin roe extracts, and inhibition assay on boiled sea urchin roe extract. nl indicates noninhibited sera; M, molecular weight; P, protein staining.
concentration was determined with the Coomasie Plus Protein Assay (Pierce). The shrimp and roe proteins separated by SDS-PAGE were electrophoretically transferred onto Immobilon-P membranes (Millipore) [8]. After blocking, the membranes were incubated with sera from individual patients and a nonatopic control. Iodine 125–labeled goat anti-human IgE (DiaMed) was used as the secondary antibody. The membranes were exposed to Kodak Imaging Film (Carestream Health Inc) for 4 to 8 days.

All 10 individuals recognized multiple proteins in the shrimp extracts (Figure 1A), but only 6 showed IgE-binding to a 38-kDa protein in the boiled urchin roe extract. Just 1 individual showed faint recognition of a high molecular weight protein. Almost no protein was recognized in the raw urchin roe (Figure 1B). To identify the immunoreactive urchin protein, an inhibition assay was performed with pooled sera from 3 individuals who recognized the band. Tropomyosin and arginine-kinase, as shrimp allergens of a similar molecular weight that might be implicated in cross-reactivity, were used as inhibitors. The pool (1:20) was preincubated at room temperature for 2 hours with recombinant tropomyosin (Lit v 1), arginine-kinase (Lit v 2), and Cor a 9 as a control (100 ng/μL). Then IgE immunolabeling using a boiled sea urchin roe membrane was performed. Tropomyosin partially inhibited IgE binding (Figure 1B). Several isoforms of tropomyosin have been described in urchin eggs [9]. A tropomyosin-like protein of sea urchin (Strongylocentrotus purpuratus) (XP_001192266) showed only 22% sequence identity and 35% similarity with Lit v 1 (ACB38288.1). Such values are lower than those observed between mollusk and shrimp tropomyosins [1]. Since clinical cross-reactivity between shrimp and mollusks is estimated around 15%, for sea urchin it might be less.

Our study shows that some shrimp-allergic patients recognize 1 protein in boiled sea urchin roe and that this protein cross-reacts with shrimp tropomyosin. These patients, therefore, may be at risk of allergic reactions when consuming roe. Since most individuals did not recognize any proteins in raw roe, its ingestion may be safe. An oral challenge with boiled and raw forms of sea urchin roe would help to determine the clinical implications of these findings in shrimp-allergic subjects that wish to consume this food, especially in its boiled form.

References


I Manuscript received October 13, 2011; accepted for publication, January 17, 2012.

Rosalía Ayuso
Mt Sinai School of Medicine
One Gustave L. Levy Place, Box 1198,
New York, NY 10029
USA
E-mail: rayuso2001@yahoo.com
Anaphylactic reactions caused by stings are a common medical problem. Onset is acute, with both local and systemic symptoms. In the United States, an estimated 20 to 50 people die every year as a result of severe anaphylaxis after bee, wasp, and ant stings [1].

Allergen immunotherapy has been used in the management of allergy for nearly 100 years. Various venom immunotherapy (VIT) schedules have been designed to treat anaphylaxis [2]. Patients who undergo rapid dose increases and patients treated with bee venom are at increased risk of side effects [3].

We report on a possible side effect of VIT, namely, Jessner lymphocytic infiltrate (also known as Jessner-Kanof syndrome and Jessner pseudolymphoma). This T-cell pseudolymphoma of the skin is an uncommon condition that presents as recurrent asymptomatic papules and plaques with benign coat sleeve–like accumulations of perivascular lymphoid cells on the face, neck, and upper back [4].

A 61-year-old man was followed by our Immunology Service because of an immediate-type reaction to bee sting that was managed with VIT. His medical history was unremarkable, and he reported that he was taking no medications and was a heavy smoker and social drinker.

The patient experienced an anaphylactic reaction 25 minutes after a bee sting, with gradual onset of symptoms. He was admitted to our emergency department in September 2008 with severe dyspnea, wheezing, urticaria, and hypotension (60/35 mmHg). His symptoms began to improve within 2 hours of receiving adrenaline, antihistamines (H1 and H2), prednisolone, intravenous infusion fluid, and nasal oxygen supplementation. During the previous year, he had experienced 3 minor local allergic reactions after being stung, although he was not classed as being allergic to venom.

Diagnosis of venom-specific allergy was confirmed by skin tests and elevated venom-specific serum IgE level.

An 8-week VIT regimen was started 45 days after the anaphylactic episode. No premedication was administered, and the initial dose was 0.01 μg, which was increased at weekly intervals. All injections were applied subcutaneously to the outside of the upper arm. The VIT regimen continued with no interruptions of regular weekly injections, although the patient reported symptoms after every injection and severe itching 4-6 hours after the third injection. Physical examination revealed erythematous papules and plaques on his chest and back that lasted for 3 days and subsequently disappeared. He was prescribed antihistamines and topical corticosteroids; however, remission was partial, and the lesions flared.

The type of lesions and their location supported the diagnosis of Jessner lymphocytic infiltrate. The results of a complete blood count, blood biochemistry, and liver function tests were normal, as was the erythrocyte sedimentation rate. The results of autoantibody tests (antinuclear antibody, C3, C4, and rheumatoid factor) were also negative. Histopathology of 1 of the lesions on his back revealed a normal epidermis with no hyperkeratosis, atrophy, or interface changes. The dermis contained moderately dense, perivascular, diffuse infiltrates composed of small, mature lymphocytes that involved the superficial and deep vascular plexuses. The infiltrate extended around the pilosebaceous follicles (Figure, A). Alcian blue staining revealed dermal mucin between the collagen bundles (Figure, B). Periodic acid-Schiff staining revealed no basal vascular changes (Figure, C). The cytoplasm and membrane of lymphoid cells stained positive for CD3 using mouse monoclonal antibody (Novocastra, NCL-L-CD3-565 [dilution 1:70]) (Figure, D).

As symptoms worsened after each injection, the VIT protocol was stopped. It was restarted 4 weeks later with premedication consisting of cetirizine dihydrochloride. After the first injection, the patient experienced local reactions, including itching and inflammation (wheal of <5 cm in diameter) around the injection site. No reactions were observed during subsequent sessions, and symptoms had resolved completely at subsequent follow-up visits.

The side effects of VIT range from localized irritation to potentially fatal anaphylaxis. Consequently, clinicians must attempt to prevent such reactions or take all the necessary steps to manage those that do occur [5].

Local reactions occur in approximately 1 case in every 200 to 500 injections and include transient wheals (urticaria), swelling at the injection site, sneezing, rhinorrhea, and ocular pruritus [6]. Systemic allergic reactions to VIT occur in about 6% of patients, although no cases of Jessner lymphocytic infiltrate or
death due to this procedure have been reported. Systemic reactions may progress to anaphylaxis [3,7].

Jessner lymphocytic infiltrate of the skin can resolve spontaneously without scarring, although it is generally persistent, with an increasing number of lesions. It is also thought to be a dermal variant of systemic lupus erythematosus [4-8]; however, the exact etiology is unknown. In the case we report, systemic lupus erythematosus was ruled out by clinical examination and a negative antinuclear antibody test result. Infection has been suggested as an etiological factor, as has photosensitivity, since exposure to sunlight can irritate or aggravate the disease [4-8]. Familial cases are rare [9].

Our patient was diagnosed with Jessner lymphocytic infiltrate 3 weeks after initiation of VIT. His lesions flared after each injection, thus indicating an association between therapy and the disease. The fact that the lesions resolved when treatment was stopped seems to support this association.

To our knowledge, this is the first report of Jessner lymphocytic infiltrate as a side effect of venom immunotherapy. We urge clinicians to be aware of this side effect in similar cases.

References


Mentha spicata is a member of the Lamiaceae family (formerly, Labiatae), which also includes other aromatic plants of genera such as Thymus vulgaris (thyme), Rosmarinus officinalis (rosemary), Ocimum basilicum (basil), and Origanum vulgare (oregano). The genus Mentha includes 20 to 30 true species, as well as numerous hybrids, the best-known of which are M spicata (hybrid between Mentha suaveolens and Mentha longifolia) and Mentha piperita (which results from a cross between M spicata and Mentha aquatica) [1]. M spicata is a common evergreen plant that grows all over Europe and the United States. The essential oil extracted from its leaves is widely used in the food, pharmaceutical, and cosmetics industries [2].

Several cases of mint hypersensitivity have been reported in the literature, including type IV hypersensitivity reactions caused by contact with mint-flavored toothpaste [3], application of compresses soaked in fresh mint leaf infusion [2], and ingestion of tea brewed from leaves of Mentha pulegium [4], as well as occupational contact urticaria, caused by M pulegium [1]. The culprit allergens in these cases were carvone, limonene, and menthol [2].

Fresh leaves of M spicata are frequently used in salads and in cooked foods; however, immunoglobulin (Ig) E-mediated reactions after ingestion of mint seem to be rather unusual. Paiva et al [5] recently described a case of IgE-mediated anaphylaxis caused by M piperita associated with toothpaste.

We present the case of a 41-year-old female teacher with a history of rhinoconjunctivitis associated with exposure to house dust mite and cat. The patient was referred to our department for recurrent episodes of uvalar angioedema that appeared a few hours after ingestion of fresh mint leaves (used as a condiment) or inhalation of mint essence during a massage. The reactions resolved with antihistamine treatment. Notably, the patient did not report a history of reactions related to ingestion of other foods, including aromatic herbs from the mint family, or cutaneous reactions in the areas where the mint essence was applied.

Skin prick tests were performed using commercial extracts of common food allergens and aeroallergens (Stallergènes), with positive results for Dermatophagoides pteronyssinus, Dermatophagoides farinae, and dog and cat epithelium. Prick-by-prick testing was performed with fresh mint leaves, since neither a commercial mint extract for prick testing nor radioallergosorbent tests (RAST) were available. The results of prick-by-prick testing and RAST with substrates of other members of the Lamiaceae family (oregano, rosemary, basil, and thyme) were all negative. Moreover, in order to achieve a more complete diagnosis, patch tests were performed with the standard series of the Italian Society

ALTERNA. 2012; V ol. 22(4): 286-312 © 2012 Esmon Publicidad
**Figure.** Immunoblotting analysis of Mentha spicata protein extract. Sodium dodecyl sulfate polyacrylamide gel electrophoresis of 27 μg of extract performed under reducing conditions (80 V, 2 hours) revealed approximately 18 discrete bands (lane A). After blotting to a nitrocellulose membrane, which was incubated overnight at 4°C with the patient’s serum, addition of the secondary antibody revealed a single immunoreactive band, with an apparent molecular weight of 50 kDa (lane B). Lane M, molecular markers (Kaleidoscope prestained standards, broad range, BioRad).

of Allergology, Occupational and Environmental Dermatology (SIDAPA), fresh mint leaves, and mint extract. The results of all tests were negative. The patient refused to undergo a bronchial provocation test with mint essence.

The prick-by-prick test and patch test with fresh mint leaves and mint extract, respectively, were also performed in 10 healthy controls, with negative results.

A protein extract was then obtained from mint leaves (5.96 mg/mL). After staining with Coomassie Colloidal Blue 0.1%, the gel electrophoresis profile (Bis Tris Nupage, Invitrogen) revealed bands of molecular weight ranging from approximately 6 to 62 kDa (Figure).

For immunoblotting, the proteins were transferred to a nitrocellulose membrane (Schleicher & Schuell BioScience) (pore size 0.45 μm; 25 V for 1.5 hours)—saturated as described elsewhere [6]—and incubated overnight with the patient’s serum. Goat antihuman IgE antibody conjugated with peroxidase (1:1000 in saturation buffer) was then added. After 2 hours, specific IgE binding was revealed by chemiluminescence, showing a single immunoreactive band of approximately 50 kDa (Figure).

In conclusion, the positive prick-by-prick results with fresh mint leaves and specific IgE binding to a protein with a molecular weight of approximately 50 kDa detected by immunoblotting led us to assume that an IgE-mediated mechanism was responsible for the reactions experienced by our patient. Therefore, as a preventive measure, the patient was advised to avoid both ingestion of fresh mint leaves and exposure to preparations in which mint is used as a flavoring ingredient. Finally, to our knowledge, this is the first time that a 50-kDa protein has been recognized as an allergen in fresh mint. Further allergen characterization studies are necessary in order to determine whether this protein could be proposed as a major mint allergen.

**Acknowledgments**

This work was supported by the University of Bari – Aldo Moro (Fondi di Ateneo, Es. Fin. 2010) and by Regione Puglia (Reti di Laboratori Pubblici di Ricerca, Progetto LAIFF).

**References**

Variations in TGF-β, IL-10, and IL-17 After Specific Immunotherapy and Correlations With Symptoms in Patients With Allergic Rhinitis

Q Qiu,1 H Lu,2 C Lu,1 S Chen,1 H Han1
1 Department of Otolaryngology, Guangdong General Hospital, Guangdong Academy of Medical Science, Guangzhou, China
2 Department of Otolaryngology, Shantou Central Hospital, Shantou, China

Key words: Allergic rhinitis. Specific immunotherapy. TGF-β. IL-10. IL-17.

Palabras clave: Rinitis alérgica. Inmunoterapia específica. TGF-β. IL-10. IL-17.

Interleukin (IL) 10, IL-17, and transforming growth factor (TGF) β play an important role in the pathogenesis of allergic rhinitis (AR); however, their role in specific immunotherapy (SIT) for AR and correlation with symptoms remain unknown. Our study analyzed nasal symptoms and compared variations in IL-10, TGF-β, and IL-17 levels before and after SIT in patients with AR in order to assess their role in SIT.

The study population comprised 48 patients (26 males and 22 females) aged 7 to 42 years (mean, 23.5 years) with perennial AR from the Otolaryngology Department of Guangdong General Hospital from March to December, 2008. The diagnostic criteria applied were from ‘Principles of diagnosis, therapy and recommendation for allergic rhinitis,’ drafted at the 2004 Lanzhou Convention [1]. Skin prick test results were positive mainly for house dust mite. Patients with an intense positive response served as indicators to assess the efficacy of SIT at 2 years.

The discovery of regulatory T cells (Treg) and type 17 helper T cells (Th17) complemented the Th1/Th2 balance hypothesis [2]. As the major immunosuppressive cytokines secreted by Tregs, IL-10 and TGF-β exhibit extensive action by inhibiting the release of proinflammatory cytokines, including suppression of antigen-presenting cells, and indirectly inhibiting cellular response and secretion of specific IgE. Additionally, both cytokines could stimulate synthesis of IgG4 and downregulate airway inflammation, thus suppressing the development of AR.

In contrast, downregulation of IL-10 and TGF-β in vivo could lead to allergic disorders [3]. The decrease in serum IL-10 and TGF-β levels, together with the negative correlation with nasal symptoms, suggests that low expression of both cytokines might cause nasal inflammation in individuals with AR.

Interleukin (IL)10, IL-17, and transforming growth factor (TGF)-β play an important role in the pathogenesis of allergic rhinitis (AR); however, their role in specific immunotherapy (SIT) for AR and correlation with symptoms remain unknown. Our study analyzed nasal symptoms and compared variations in IL-10, TGF-β, and IL-17 levels before and after SIT in patients with AR in order to assess their role in SIT.

The mean (SD) symptom score (P<0.05) in patients with AR was (9.73 [1.22]), (4.42 [1.36]), and (3.91 [1.29]) at baseline and at 1 and 2 years after SIT. Variations in IL-10, TGF-β, and IL-17 at baseline and at 1 and 2 years are shown in the Figure.

A negative correlation was also found between serum IL-10 and TGF-β (r=–0.34, P<0.05; r=–0.31, P<0.05) and symptom scores at 2 years after SIT. However, no correlation was found between these levels and symptom scores at 1 year after SIT (P>0.05). The level of IL-17 was positively correlated with symptom scores (r=0.57, P<0.05) and maintained the positive correlation at 2 years (r=0.52, P<0.05). However, no correlation was revealed at 1 year (P>0.05). Our results indicate that IL-10, TGF-β, and IL-17 could serve as indicators to assess the efficacy of SIT at 2 years.

The discovery of regulatory T cells (Treg) and type 17 helper T cells (Th17) complemented the Th1/Th2 balance hypothesis [2]. As the major immunosuppressive cytokines secreted by Tregs, IL-10 and TGF-β exhibit extensive action by inhibiting the release of proinflammatory cytokines, including suppression of antigen-presenting cells, and indirectly inhibiting cellular response and secretion of specific IgE. Additionally, both cytokines could stimulate synthesis of IgG4 and downregulate airway inflammation, thus suppressing the development of AR.

As for treatment, SIT remains the only available approach that alters the natural progress of allergic disorders through immunomodulation [7]. Since the local cytokine profile is more likely to change, serum cytokine level may better reflect the condition of the immune system. Increased serum IL-10 level is considered indicative of the success of SIT, while the role of TGF-β remains open to debate [8]. As our results indicate, a significant improvement in serum IL-10 and TGF-β levels was observed over 2 years after SIT.

Prior to SIT
1-Year SIT
2-Year SIT

Figure. Variations in IL-10, TGF-β, and IL-17. SIT indicates specific immunotherapy; IL, interleukin; TGF, transforming growth factor.

*Compared with normal controls, P<0.05
**Compared with AR patients prior to SIT, P<0.05
***Compared with AR patients 1 year after SIT, P<0.05
a 2-year treatment period compared with levels at baseline. The negative correlation with symptoms indicates that both cytokines are involved in immunomodulation, thereby diminishing airway hyperresponsiveness and suppressing allergic inflammation. However, the expression of both IL-10 and TGF-ß after 2 years of treatment was lower than after 1 year of treatment, probably because of the gradual return to a balanced immune system and the relatively low baseline level. The reduction in IL-17 expression at 2 years of SIT compared with 1 year indicated that immunotherapy might downregulate expression of IL-17. Besides, the finding of lower IL-10, TGF-ß, and IL-17 levels than in controls after 2 years of treatment seemed to be correlated with the re-establishment of immunity over time. Longer duration of immunotherapy could be associated with a more significant improvement in symptoms and superior efficacy. In conclusion, IL-10, TGF-ß, and IL-17 play a vital role in the pathogenesis of AR and the response to SIT. Factors leading to variations and underlying mechanisms should be further investigated.

References


Manuscript received January 14, 2012; accepted for publication March 6, 2012.

Dr Qianhui Qiu
Department of Otolaryngology
Guangdong General Hospital
Guangdong Academy of Medical Science
Guangzhou 510080
China
E-mail: qiuqianhui@hotmail.com