Dose-Dependent Anaphylaxis to Orange Juice Without Detectable Specific Immunoglobulin E

V Vovolis, N Koutsostathis
Department of Allergy and Clinical Immunology, Laiko General Hospital, Athens, Greece

Key words: Orange. Allergy. Anaphylaxis. Food allergy.

Palabras clave: Naranja. Alergia. Anafilaxia. Alergia alimentaria.

Immediate allergic reactions to orange are rare and immunoglobulin (Ig) E–mediated [1]. We report the case of a 28-year-old man with anaphylaxis induced by fresh orange juice. The reaction was dose-dependent and could only be confirmed by challenge test, because specific IgE to orange was undetectable by skin prick test (SPT) and CAP immunoassay. The patient had experienced identical anaphylactic reactions on 2 occasions within 20 minutes after consumption of 300 mL of fresh orange juice. The symptoms were feeling of heat, flushing, itching on the palms and head, rhinitis, and generalized urticaria. His history was remarkable in that he had no symptoms when he ate 2 oranges or drank 300 mL of a commercial orange juice product.

The patient was not suffering from allergic disease (asthma, rhinitis, atopic dermatitis) and had negative SPT results to aeroallergens and common food allergens. Surprisingly, SPT results with commercial extract and fresh juice of all citrus family members (orange, lemon, mandarin, and grapefruit) were also negative, as was an intradermal test with filtered orange juice. Specific IgE to orange, lemon, mandarin, rPru p 3 (lipid transfer protein) and profilin was not identified by CAP immunoassay (Phadia, Uppsala, Sweden).

A challenge test was performed with fresh orange juice administered at increasing doses (50, 100, 150, 200, 300 mL) every 30 minutes. Within 20 minutes of drinking 150 mL of fresh orange juice the patient experienced an anaphylactic reaction with generalized urticaria similar to that reported in his history. The same reaction also appeared after 30 minutes with 150 mL of lemon, mandarin, and grapefruit juice. An oral challenge test with 2 commercial orange juice products was positive at 600 mL and 800 mL, respectively. A provocation test with fresh orange juice boiled for 2 minutes induced a mild anaphylactic reaction at 500 mL, thus demonstrating that the offending allergen is heat-labile but not completely inactivated by boiling.

Allergic reactions to orange are rare, and manifestations range from oral allergy syndrome to mainly IgE-mediated anaphylaxis [2,3]. The case we report is unique because a dose-dependent anaphylactic reaction to orange juice occurred with no detectable specific IgE to orange. In our case, a carefully performed open challenge test with fresh orange juice proved to be the only reliable procedure for the diagnosis to be established. Our patient experienced anaphylactic reactions whenever he consumed more than 150 mL of fresh orange juice. The provocation test indicated that the offending allergen exists in all other fresh citrus fruit juices. This finding is consistent with the results of other immunodetection studies with allergens [4,5].

We showed that the culprit allergen in our study was at least partly heat-labile, because the patient reacted only after consuming a large amount (500 mL) of boiled orange juice. This allergen does not belong to any of the 3 recently identified major orange allergens—profilin (Cit s 2), germin-like protein (Cit s 1), and lipid transfer protein (Cit s 3)—because these were all found to be heat-resistant [1-3].

The culprit allergen is likely to be uncovered after proteolytic degradation of certain unknown orange proteins (pro-allergen) during digestion. This is a reasonable explanation why specific IgE to orange allergen was undetectable in this patient. A similar mechanism has been proposed for anaphylaxis to sesame seed in patients with a negative SPT result [6]. Moreover, extremely low sensitivity to orange in this case—the patient tolerated 100 mL of fresh orange juice–-could affect the diagnostic sensitivity of SPT.

We can infer that anaphylaxis to orange juice occurs as a dose-dependent reaction with no detectable specific IgE to orange. A challenge test in this case was the only reliable diagnostic technique that was more sensitive than SPT with fresh juice. The culprit allergen was partly heat-labile and found to exist in all other citrus fruits.

References

1. Ahrazem O, Ibanez MD, Lopez-Torrejon G, Sanchez-Monge R, Sastre J, Lombardero M, Barber D, Salcedo G. Lipid transfer proteins and allergy to oranges. Int Arch Allergy Immunol. 2005;137:201-10.
2. Crespo JF, Retzek M, Foetisch K, Sierra-Maestro E, Cid-Sanchez AB, Pascual CY Conti A, Feliu A, Rodriguez J, Vieths S, Scheurer S. Germin-like protein Cit s 1 and profilin Cit s 2 are major allergens, in orange (Citrus sinensis) fruits. Mol Nutr Food Res. 2006;50:282-90.
3. Ebo DG, Ahrazem O, Lopez-Torrejon G, Bridts CH, Salcedo G, Stevens WJ. Anaphylaxis from Mandarin (Citrus reticulata): Identification of potential responsible allergens. Int Arch Allergy Immunol. 2007;144(1):39-43
4. Lopez-Torrejon G, Ibanez MD, Ahrazem O, Sanchez-Monge R, Sastre J, Lombardero M, Barber D, Salcedo G. Isolation, cloning and allergenic reactivity of natural profiling Cit s 2, a major orange allergen. Allergy. 2005;60:1424-9.
5. Ahrazem O, Ibanez MD, Lopez-Torrejon G, Sanchez-Monge R, Sastre J, Lombardero M, Barber D, Salcedo G. Orange germin-like glycoprotein Cit s 1: an equivocal allergen. Int Arch Allergy Immunol. 2006;139:96-103.
6. Leduc V, Moneret-Vautrin DA, Tzen JT, Morisset M, Guerin L, Kanny G. Indentification of oleosins as major allergens in sesame seed allergic patients. Allergy. 2006;61(3):349-56.

Manuscript received April 8, 2009; accepted for publication May 28, 2009.

Vasilios Vovolis, MD, PhD
Department of Allergy and Clinical Immunology
Laiko General Hospital
Agiou Thoma 17, Goudi, Athens, Greece
E-mail: vasvovolis@gmail.com

Sclerosing Cholangitis Associated With Good Syndrome

T Kampitak, P Putiworanat, H Chantaphakul, J Klaewsongkram
Division of Allergy and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Key words: Good syndrome. Immunodeficiency. Sclerosing cholangitis. Thymoma.

Palabras clave: Síndrome de Good. Inmunodeficiencia. Colangitis esclerosante. Timoma.

Sclerosing cholangitis is a chronic cholestatic liver disease characterized by inflammation, fibrosis, and stricture of the bile ducts. It is classified as primary and, less commonly, secondary. Diagnosis of primary sclerosing cholangitis requires the exclusion of various conditions including immunodeficiency-related disorders [1]. The main primary and secondary immunodeficiency diseases associated with sclerosing cholangitis are hyperimmunoglobulin M syndrome and AIDS, respectively. To date, only 1 asymptomatic case of sclerosing cholangitis in association with Good syndrome has been reported [2]. We describe a case of Good syndrome associated with sclerosing cholangitis and multiple recurrent opportunistic infections.

In 2000, a previously healthy 42-year-old man presented with chronic cough and weight loss. Chest X-ray revealed a large mediastinal mass. The mass was resected and histopathology testing revealed a benign encapsulated thymoma (medullary type). The patient later experienced a few episodes of pneumonia, one of which was due to *Streptococcus pneumoniae*, resulting in chronic bronchiectasis. He also experienced multiple episodes of herpes zoster and oral candidiasis.

In June 2007, he was admitted due to a 1-week history of fever with abdominal pain, which followed a 1-month history of progressive jaundice. Physical examination revealed hepatomegaly with tenderness. Laboratory tests disclosed the following values: hemoglobin 9.5 g/dL, white cell count 9620/μL (polymorphonuclear cells 86%, lymphocytes 4%), platelet count 148,000/μL, albumin 2.6 g/dL, total bilirubin 16.9 g/dL, direct bilirubin 12.8 g/dL, aspartate aminotransferase 128 U/L, alanine aminotransferase 69 U/L, alkaline phosphatase 1,610 U/L. His blood culture grew *Vibrio cholerae* non-O1 and stool examination was negative for *Cryptosporidium*.

Computed tomography of the abdomen revealed hepatomegaly and mild dilatation of intrahepatic ducts with no definite mass. Endoscopic retrograde cholangiopancreatography revealed multiple microabscesses communicated with small branches of the intrahepatic ducts, which had a beaded and tapering appearance consistent with sclerosing cholangitis.

Additional testing revealed negative HIV-1 antibody and HIV-1 RNA levels. There was an inverted CD4/CD8 cell ratio of 0.33 with CD4 and CD8 lymphocyte counts of 168/μL (18%) and 505/μL (56%), respectively. The CD19 count was 1% (7.7%-25.4%). The patient was hypogammaglobulinemic with an immunoglobulin (Ig) G level of 445 mg/dL (reference range, 700-1600), an IgM level of <21.4 mg/dL (reference range, 40-230) and an IgA level of 28.5 mg/dL (reference range, 70-400).

These findings led us to make a diagnosis of thymoma with immunodeficiency (Good syndrome). The patient responded well to antimicrobial therapy, and immunoglobulin replacement therapy was planned in an outpatient regimen; however, he was lost to follow-up after discharge.

Good syndrome is a rare primary immunodeficiency disorder in adults. It is characterized by combined B-cell and T-cell immunodeficiency in association with thymoma. Affected patients have increased susceptibility to bacterial (particularly encapsulated organisms), viral, and fungal infections of the respiratory and gastrointestinal tracts [3-6]. To the best of our knowledge, this is the first report of Good syndrome complicated with clinically active sclerosing cholangitis.

Immunological defects in Good syndrome include hypogammaglobulinemia, few or absent B cells, an abnormal CD4/CD8 cell ratio, $CD4^+$ T-cell lymphopenia, and impaired T-cell response [1-4]. The pathogenesis of immunodeficiency in Good syndrome remains unclear. The possible mechanisms include bone marrow defects, loss of naïve or memory $CD4^+$ T cells and presence of regulatory T cells or autoantibodies as a paraneoplastic phenomenon in thymoma [3-6].

The mainstay of treatment includes removal of the thymoma, although immunodeficiency may be irreversible in some cases, such as our patient. Immunoglobulin replacement therapy is usually required for reduction of recurrent respiratory infections and pulmonary complications. Antimicrobial prophylaxis may be beneficial in patients who continue to have recurrent infections despite immunoglobulin therapy.

In conclusion, Good syndrome should be considered one of the immunodeficiency-related causes of secondary sclerosing cholangitis, particularly in patients with a history of thymoma.

References

1. Abdalian R, Heathcote EJ. Sclerosing cholangitis: a focus on secondary causes. Hepatology. 2006;44(5):1063-74.
2. Yoshioka R, Sato Y, Kogure A, Ohira H, Takagi T, Kuroda M, Miyata M, Obara K, Nishimaki T, Kasukawa R. Association of primary

sclerosing cholangitis, thymoma and hypogammaglobulinemia. Liver. 1995;15(1):53-5.
3. Kelleher P, Misbah SA. What is Good syndrome? Immunological abnormalities in patients with thymoma. J Clin Pathol. 2003;56(1):12-6.
4. Agarwal S, Cunningham-Rundles C. Thymoma and immunodeficiency (Good syndrome): a report of 2 unusual cases and review of the literature. Ann Allergy Asthma Immunol. 2007;98(2):185-90.
5. Tsai YG, Lai JH, Kuo SY, Chen HC, Chang DM. Thymoma and hypogammaglobulinemia (Good's syndrome): a case report. J Microbiol Immunol Infect. 2005;38(3):218-20.
6. Yel L, Liao O, Lin F, Gupta S. Severe T- and B-cell immune deficiency associated with malignant thymoma. Ann Allergy Asthma Immunol. 2003;91(5):501-5.

Manuscript received January 8, 2009; accepted for publication May 29, 2009.

Thatchai Kampitak, MD
Division of Allergy and Clinical Immunology
Department of Internal Medicine
Faculty of Medicine
Chulalongkorn University
1873 Rama IV Road Pathumwan
Bangkok Thailand 10330
E-mail: thatchai_k@yahoo.com

Contact Dermatitis to Antibiotic Ointments

MC Moreno Escobosa, MC Moya Quesada, S Cruz Granados, J Amat López
Department of Allergology, Hospital Torrecárdenas, Almería, Spain

Key words: Allergic contact dermatitis. Furacin. Nitrofurazone. Polyethylene glycol.

Palabras clave: Dermatitis de contacto alérgica. Furacín. Nitrofurazona. Polietilenglicol.

Antibiotic ointments are commonly used in patients with burns, chronic leg ulcers, and superficial infections, and can sometimes cause contact dermatitis. We describe 2 such cases.

Patient 1

A 44-year-old man prescribed Furacin (nitrofurazone, polyethylene glycol) to treat chronic leg ulcers developed local eczematous lesions on his legs 24 hours after application of the ointment. Similar lesions occurred following the use of Bactroban (mupirocin, polyethylene glycol [PEG]) and Dermisome tri antibiotic ointment (bacitracin, neomycin, polymyxin B). Patch tests performed with the European standard series, Bactroban, polymyxin B 3%, bacitracin 5%, nitrofurazone 1%, and PEG 4%, all in petrolatum, yielded positive reactions for neomycin on day 4 (+++), nitrofurazone on day 4 (++++), and PEG on days 2 (++) and 4 (++++). In view of the negative patch test for Bactroban, we performed a repeated open application test with this product and observed the development of an eczematous lesion in the application area.

Patient 2

A 43-year-old woman developed eczematous lesions on her hand, face, and neck 24 hours after applying Furacin, Bactroban, and Tulgrasum Antibiotico (bacitracin, neomycin, polymyxin B) to treat a burn on her hand. Patch tests performed with the European standard series, Bactroban, nitrofurazone 1%, PEG 4%, mupirocin 1% and 10%, and Tulgrasum Antibiotico, all in petrolatum, yielded positive reactions to colophony, nitrofurazone, and PEG on days 2 (++) and 4 (+++).

Both patients were diagnosed with allergic contact dermatitis to nitrofurazone and polyethylene glycol (among other compounds).

Furacin (Seid, Barcelona, Spain) is a topical antimicrobial product containing nitrofurazone 0.2% and PEG 300, PEG 1000, and PEG 4000 as vehicles. Nitrofurazone (5-nitro-2-furaldehyde semicarbazone) is a potent sensitizer that can cause severe allergic contact dermatitis, mainly in patients with chronic leg ulcers, superficial infections, burns, and other forms of chronic dermatitis [1]. In the 1980s, in a study of 390 patients from India with suspected contact dermatitis to topical drugs, Bajaj and Gupta [2] found nitrofurazone to be the most common sensitizer, with 36.2% of patients developing a positive patch test reaction. PEGs, which are condensation polymers of ethylene glycol of various molecular weights, are used extensively in the pharmaceutical industry to facilitate skin penetration. The combination of nitrofurazone, a potent allergen, and PEG, which enhances the bioavailability of topical drugs, on damaged skin predisposes patients to the development of allergic contact dermatitis [3].

Although few contact allergies to PEGs have been reported, Bajaj et al [4] showed positive patch test results to PEGs in 6.7% of patients with suspected topical drug sensitivity and the majority of these reactions were caused by PEGs with lower molecular weights. Stenveld et al [5] suggested that such PEGs were most likely to cause contact dermatitis in nitrofurazone-containing topical preparations [5]. As the main excipient in the products used by our patients was a low-molecular-weight PEG, we think that it could be responsible for sensitization, as Bajaj et al and Stenveld et al proposed.

Of the few cases reporting sensitization to PEG and nitrofurazone, Guijarro et al [6] and Prieto et al [7] published 1 and 2 cases, respectively, describing allergic contact dermatitis to Furacin with positive patch tests to nitrofurazone and PEG, as in our patients.

The fact that the periodic use of antibiotic ointments to treat chronic ulcers is likely to cause sensitization to nitrofurazone

and PEGs should be taken into account when considering the prescription of these drugs for long periods [8]. The lesions that appeared on the face and neck of patient 2 were probably caused by indirect contact through the hands.

As PEG sensitization does not appear to be uncommon, it is important to perform patch tests with all the components of topical drugs to identify the offending constituent(s). Although nitrofurazone use has declined over the years [8], it should be prescribed with care—and particularly in patients with chronic dermatitis—due to its sensitizing properties [1].

References

1. Ballmer-Weber BK, Elsner P. Contact allergy to nitrofurazone. Contact Dermatitis. 1994; 31: 274-5.
2. Bajaj AK, Gupta SC. Contact hypersensitivity to topical antibiotics. Int J Dermatol. 1986; 25:103-5.
3. De Groot AC, Conemans JM. Contact allergy to furazolidone. Contact Dermatitis. 1990; 22: 202-5.
4. Bajaj AK, Gupta SC, Chatterjee AK, Singh KG. Contact sensitivity to polyethylene glycols. Contact Dermatitis. 1990; 22: 291-2.
5. Stenveld HJ, Langendijk PNJ, Bruynzeel DP. Contact sensitivity to polyethylene glycols. Contact Dermatitis. 1994; 30: 184-5.
6. Guijarro SC, Sánchez-Pérez J, García-Díez A. Allergic contact dermatitis to PEG and nitrofurazone. Am J Contact Dermat. 1999; 10: 226-7.
7. Prieto A, Baeza ML, Herrero T, Barranco R, De Castro FJ, Ruiz J, De Barrio M. Contact dermatitis to Furacin . Contact Dermatitis. 2006; 54:126.
8. Bajaj AK, Saraswat A, Mukhija G, Rastogi S, Yadav S. Patch testing experience with 1000 patients. Indian J Dermatol Venereol Leprol. 2007; 73(5): 313-8.

Manuscript received February 7, 2009; accepted for publication June 8, 2009.

M. Carmen Moreno Escobosa
Department of Allergology
Hospital Torrecárdenas
Paraje Torrecárdenas, s/n
04009 Almería, Spain
E-mail: moreno.escobosa@terra.es

Thrombocytopenia and Iodinated Contrast

MJ García Bueno,[1] MA Tejedor Alonso[2]
[1]*Hematology Unit, Fundación Hospital Alcorcón, Alcorcón, Spain.*
[2]*Allergy Unit, Fundación Hospital Alcorcón, Alcorcón, Spain.*

Key words: Thrombocytopenia. Contrast medium. Iomeprol. Drug-induced.

Palabras clave: Trombocitopenia. Medios de contraste. Iomeprol. Inducido por drogas.

A 65-year-old woman was admitted to the emergency room with gingival hemorrhage. Twelve hours previously, she had undergone a total body computed tomography (CT) with 100 mL iomeprol (62.24 g/100 mL), an iodinated contrast medium. Twenty minutes after the procedure, the patient experienced dyspnea and a burning sensation in the head. Over the following 2 hours, she experienced headache, chills, fever (38ºC), vomiting, gingival and lingual bleeding, and petechiae and ecchymoses on the neck, legs and arms. There was no history of drug intake in the preceding year and there were no other significant physical abnormalities or clinical signs of viral infection.

Physical examination revealed the presence of petechiae and ecchymoses on the legs. The platelet count was 6×10^9/L, with normal hemoglobin and white blood cell count. Standard coagulation tests ruled out disseminated intravascular coagulation. Glucose, sodium, potassium, creatinine, aspartate aminotransferase, and alanine aminotransferase levels were normal.

After receiving 5 units of concentrated platelets, the patient made good progress and required no further treatment. The platelet count was 38×10^9/L after transfusion and 162×10^9/L 6 days later. Other tests were performed and yielded the following results: normal complement (C3, C4), tryptase, and immunoglobulin (Ig) E levels 13 and 20 hours after the reaction and negative platelet antibodies and platelet factor 4 antibodies during the reaction.

Five years earlier, the patient had been diagnosed with follicular lymphoma grade 3, stage III B. She received 9 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy, the last of which had been administered 4 years previously. At the time of the adverse reaction, the patient was in a wait and see follow-up program, with clinical and radiological controls every 4 months. In the previous 2 CT procedures, she had experienced chills and discomfort, but no signs of bleeding, 45 minutes after injection of the contrast medium.

We report a case of severe thrombocytopenia following injection of the radiographic medium, iomeprol, a phenomenon not previously reported in the literature.

The mechanism for acute thrombocytopenia due to contrast medium is essentially unknown but the event may have occurred as the result of an immunological reaction, or it may be related to the chemical properties of the contrast medium [1,2]. We believe that an immunological reaction occurred in our case as the patient had experienced chills and discomfort following 2 previous procedures.

There have been several reports of acute, severe thrombocytopenia after the injection of iodinated contrast medium in radiographic studies. The mechanisms underlying specific antibody induction are unknown, although several hypotheses have been suggested, namely, the covalent binding of hapten to the membrane protein; the binding of a drug-induced antibody to the membrane protein in the presence of soluble drug; drug-induced conformational change of glycoprotein IIb/IIIa; a drug-induced autoantibody reacting with autologous platelets; and the formation of an immune complex mediated by a drug, platelet factor 4, and a specific antibody. Unfortunately, in patients with a history of drug-induced thrombocytopenia, antibody tests may be negative [3,4,5].

We believe that thrombocytopenia due to the use of iodinated contrast media may be more common than thought, and recommend that these agents be included in the list of drugs with risk for acute thrombocytopenia.

If severe thrombocytopenia and wet purpura appear after the administration of contrast medium, they should be aggressively treated with platelet transfusions owing to the risk of fatal intracranial or intrapulmonary hemorrhage. Corticosteroids are often given, yet there is no evidence that they are helpful if the thrombocytopenia is drug-induced. Intravenous immune globulin and plasma exchange have been used in acutely ill patients but the benefit of these treatments is uncertain [5].

Once established, drug sensitivity probably persists indefinitely. As a consequence, our patient was advised to avoid radiographic contrast medium permanently.

References

1. Ural AU, Beyan A, Yalçin A. Thrombocytopenia following intravenous iopamidol. Eur J Clin Pharmacol. 1998;54:575-576.
2. Curradi F, Abbritti G, Agnelli G. Acute thrombocytopenia following oral cholecystography with iopanoic acid. Clinical toxicology. 1981;18:221-224.
3. Chang JC, Lee D, Gross HM. Acute thrombocytopenia after IV administration of a radiographic contrast medium. AJR. 1989;152:947-949.
4. Hysell JK, Hysell JW, Gray JM. Thrombocytopenic purpura following iopanoic acid ingestion. JAMA. 1977;237:361-362.
5. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. N Engl J Med. 2007;357:580-587.

Manuscript received March 23, 2009; accepted for publication, June 16, 2009.

MJ García Bueno
Fundación Hospital Alcorcón
C/ Budapest, 1
28922 Alcorcón, Spain.
E-mail: mjgarcia@fhalcorcon.es

Simultaneous SCIT With 2 Separate Allergen Extracts Demonstrates Comparable Safety Compared to SCIT With a Single Allergen Extract

A Röder, N Darrelmann, W Klingenberg, M Krüll, N Suttorp, O Noga
Respiratory and Infectious Diseases, Charité-Universitätsmedizin Berlin, Germany

Key words: SCIT. Safety. Simultaneous.

Palabras clave: ITSC. Seguridad. Simultánea.

Allergic rhinoconjunctivitis and allergic asthma are common diseases of increasing prevalence affecting approximately 25% of the population in developed countries [1]. Subcutaneous immunotherapy (SCIT) is a well-described treatment for moderate to severe allergic rhinitis and allergic asthma [2,3,4]. Furthermore, it is well established that immunotherapy is the only disease-modifying therapy in allergic rhinitis and asthma. The preventive effect of SCIT on the development of allergic asthma has been proven, even years after the discontinuation of therapy [5]. If a strict protocol [6] is used and all the criteria for including and excluding patients are fulfilled, SCIT can be regarded as safe [7].

Many patients are sensitized to more than 1 allergen. Due to the need for a limited number of single allergens in allergen extracts, many of these cannot be treated satisfactorily with SCIT. The simultaneous administration of 2 allergen extracts provides a possibility to achieve high allergen doses in polysensitized patients. The aim of this study was to compare the safety of SCIT using 2 separate allergen extracts administered simultaneously to that of standard SCIT with a single allergen extract.

Seventy-seven patients with symptoms of birch or grass pollen allergy were selected from the outpatients department after undergoing examination, a skin prick test, and measurement of specific immunoglobulin (Ig) E. Over

Table. Summary of Adverse Events and Side Reactions

	Total (n=77)	Simultaneous SCIT (Birch and Grass) (n=25)	Standard SCIT (Birch) (n=29)	Standard SCIT (Grass) (n=23)
	No. (%)	No. (%)	No. (%)	No. (%)
All adverse events	53 (68.8)	15 (60)	23 (79.3)	15 (65.2)
No adverse events	8 (10.4)	5 (20)	2 (7)	1 (0.67)
Local side reaction	47 (61)	14 (56)	19 (82.6)	14 (60.9)
Grade I reaction	4 (5.2)	0 (0)	3 (10.3)	1 (4)
Grade II reaction	2 (2.6)	1 (4)	1 (3.5)	0 (0)
Grade III reaction	0 (0)	0 (0)	0 (0)	0 (0)
Grade IV reaction	0 (0)	0 (0)	0 (0)	0 (0)

a period of 1 year, all the patients were treated with health authority–approved allergen extracts for specific SCIT (NHD; Allergopharma, Reinbeck, Germany). Of these patients, 25 received simultaneous SCIT with 2 allergen extracts and 52 received a standard single extract (29 for birch pollen and 23 for grass pollen). Based on a patient questionnaire, 86% reported side reactions. These were reported by 75% of the patients that had received simultaneous SCIT, 92% of those treated with standard birch pollen SCIT, and 93.75% of those treated with standard grass pollen SCIT.

The majority of the reported side reactions were clinically mild. On a 6-point scale from 0 to 5 according to the European Academy of Allergy and Clinical Immunology (EAACI) rating [8] for the severity of side reactions, the patients treated with simultaneous SCIT scored a mean severity of 1.25, corresponding to local reactions only (eg, local erythema or itching). The mean severity scores for the birch pollen and grass pollen groups were 1.4 and 1.25, respectively. No statistically significant differences were found between the groups, meaning that a generally low level of adverse events in simultaneous or standard SCIT can be assumed. More severe reactions were rare and between-group differences were also insignificant in this respect (Table).

SCIT is an effective disease-modifying treatment strategy [5]. The use of simultaneous SCIT is widespread in clinical praxis as a suitable treatment for patients sensitized to both birch and grass pollen is much needed. Two allergen extracts are required in order to achieve high doses of allergen and the cumulative dose is critical to an optimal outcome.

In this study we have demonstrated that the administration of 2 separate allergen extracts in patients with multiple allergies to pollen is safe, with no severe side effects observed. Side reactions were mild, and compared with standard SCIT with birch or grass pollen, there were no significant differences in terms of the number or severity of events. None of the patients needed to be treated with epinephrine. The sample size was not sufficient to accurately analyze the exact rate of side reactions due to the small number of reactions observed. SCIT with 2 separate allergen extracts therefore does not seem to be correlated with a higher incidence of adverse events.

References

1. Devereux G. The increase in the prevalence of asthma and allergy: food for thought. Nat Rev Immunol. 2006 Nov;6(11):869-74.
2. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, Till SJ, Hamid QA, Nouri-Aria KT. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med. 1999 Aug 12;341(7):468-75.
3. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev. 2007 Jan 24;(1).
4. Hedlin G, Wille S, Browaldh L, Hildebrand H, Holmgren D, Lindfors A, Nordvall SL, Lowenstein H. Immunotherapy in children with allergic asthma: effect on bronchial hyperreactivity and pharmacotherapy. J Allergy Clin Immunol. 1999 Apr;103(4):609-14.
5. Möller C, Dreborg S, Ferdousi HA, Halken S, Høst A, Jacobsen L, Koivikko A, Koller DY, Niggemann B, Norberg LA, Urbanek R, Valovirta E, Wahn U. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol. 2002 Feb;109(2):251-6.
6. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E; EAACI, Immunotherapy Task Force. Standards for practical allergen-specific immunotherapy. Allergy. 2006;61
7. Winther L, Arnved J, Malling HJ, Nolte H, Mosbech H. Side-effects of allergen-specific immunotherapy: a prospective multi-centre study. Clin Exp Allergy. 2006 Mar;36(3):254-60.
8. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol. 1998 Oct;102(4 Pt 1):558-62.

Manuscript received June 10, 2009; accepted for publication, July 3, 2009.

Oliver Noga
Department of Internal Medicine, Infectious Diseases and Respiratory Medicine
Allergy and Asthma Clinic, Charité-Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin, Germany
E-mail: oliver.noga@charite.de

Recent-Onset Bronchial Asthma as a Manifestation of Systemic Mastocytosis

JN Sancho-Chust, E Chiner, A Camarasa, M Llombart
Pulmonology Section, Hospital Universitari Sant Joan d'Alacant, Alacant, Spain

Key words: Asthma. Bronchial hyperresponsiveness. Mast cell disease. Nedocromil. Systemic mastocytosis.

Palabras clave: Asma. Hiperreactividad bronquial. Mastocitosis. Nedocromil. Mastocitosis sistémica.

Introduction

Mastocytosis is characterized by the excessive growth and accumulation of mast cells. While cutaneous mastocytosis is limited to the skin, systemic mastocytosis involves extracutaneous organs [1]. Respiratory involvement is unusual and little has been reported about the underlying etiopathogenic mechanisms [2-7].

Case Description

A 58-year-old woman with cutaneous mastocytosis reported an increase in cutaneous lesions and paroxystic events such as abdominal pain, diarrhea and respiratory symptoms.

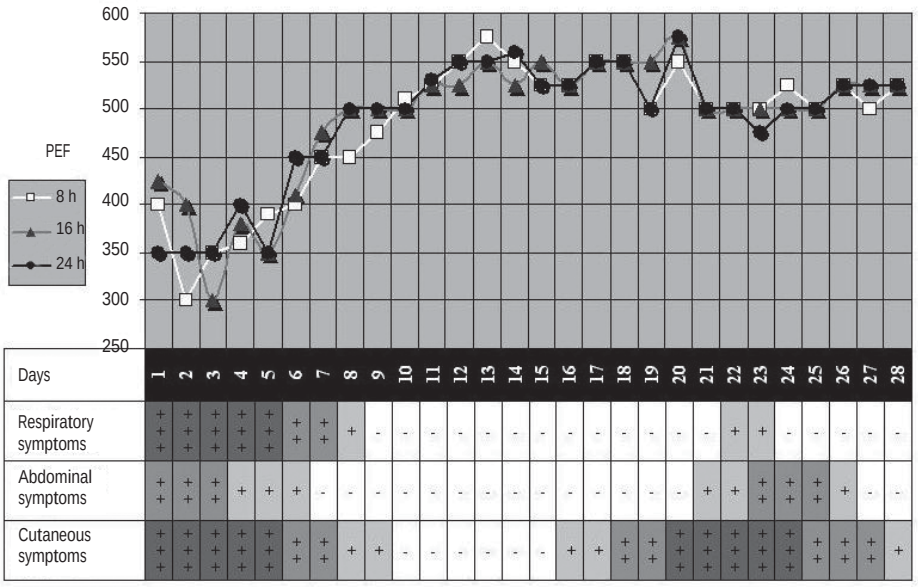

Figure. Symptom diary and peak expiratory flow (PEF) (L/min) of the patient in the first 4 weeks of treatment with nedocromil. The relation between respiratory, gastrointestinal, and cutaneous symptoms can be seen. A relatively greater improvement in respiratory symptoms compared to other manifestations can also be seen.

After complementary exams, she was diagnosed with systemic mastocytosis.

In view of her respiratory symptoms, the patient was referred to our clinic for evaluation. No personal or family history of asthma, rhinitis, or atopy were reported. She reported dry cough, dyspnea, and self-audible wheezing of gradual onset during the day and night in addition to gastrointestinal and skin symptoms that had occurred practically daily over the previous 3 months.

Serum tryptase was 61 mcg/L. Spirometry was normal, with a negative bronchodilation test. Total serum immunoglobulin (Ig) E levels and a radioallergosorbent test (RAST) performed for standard airborne allergens were normal. Methacholine bronchial provocation was positive, with a 20% decrease in forced expiratory volume in 1 second from baseline (PC20) caused by 10.3 mg/mL of methacholine.

Inhaled corticosteroids (budesonide, 400 mcg/12 h), oral leukotriene receptor antagonists (montelukast 10 mg/24 h) and oral disodium cromoglycate (800 mg/24 h) were added to the treatment.

At the following clinical check-up, the respiratory symptoms persisted and the PC20 had risen to 11 mg/mL. It was decided to add an inhaled mast cell stabilizer (MCS) (sodium nedocromil 4 mg/12 h) to the treatment and the patient was given a device to measure peak expiratory flow and asked to keep a symptom diary.

At subsequent checkups, the cutaneous lesions had improved, and the gastrointestinal and respiratory symptoms had disappeared. The diary (Figure) showed the relationship between respiratory, clinical, and functional involvement and other manifestations. The PC20 was 25 mg/mL. The dose of budesonide was decreased to 200 mcg/12 h and an optimum control of symptoms was maintained.

Discussion

Levels of histamine, prostaglandin D2, and tryptase in the bronchoalveolar lavage fluid of asymptomatic patients with asthma have been found to correlate with bronchial hyperresponsiveness [8], and there is mast cell infiltration in the airways of patients with asthma but not eosinophilic bronchitis [9].

In view of the above, it seems logical to assume that patients with symptomatic mastocytosis will tend to have bronchial hyperresponsiveness. Nevertheless, very few cases have been described [2-7]. The case we describe has some peculiarities. An association between systemic mastocytosis and clinical and functional respiratory deterioration was observed. IgE levels, RAST results, and a lack of any relevant clinical history makes it unlikely that an atopic component was responsible for the bronchial hyperresponsiveness. Furthermore, the bronchial provocation test remained the same after treatment with inhaled corticosteroids. The most important indication that bronchial hyperresponsiveness was related to mast cell infiltration, however, was the clear improvement in hyperresponsiveness following treatment with MCS.

Nedocromil acts on 3 levels: it stabilizes mast cells, decreases the permeability of the pulmonary microvasculature, and prevents epithelial damage in the airway [10]. MCSs thus have a selective effect on the key etiopathogenic events in systemic mastocytosis involving the lungs. To the best of our

knowledge, this relation has not been described previously, possibly because respiratory symptoms are uncommon.

In conclusion, bronchial hyperresponsiveness in patients with systemic mastocytosis appears to bear a relation to other clinical manifestations of the disease. Therefore, all patients with systemic mastocytosis should be systematically evaluated for the presence of bronchial hyperresponsiveness. This important management strategy would ensure that such patients would benefit from a safe, effective treatment of their respiratory symptoms.

References

1. Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, Marone G, Nuñez R, Akin C, Sotlar K, Sperr WR, Wolff K, Brunning RD, Parwaresch RM, Austen KF, Lennert K, Metcalfe DD, Vardiman JW, Bennett JM. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res. 2001;25:603-25.
2. Stutzman L, Zsoldos S, Ambrus JL, Asboe-Hansen G. Systemic mast cell disease: physiologic considerations and report of a patient treated with nitrogen mustard. Am J Med. 1960;37:894-901.
3. Demis J. The mastocytosis syndrome: clinical and biological studies. Ann Intern Med. 1963;59:194-9.
4. Mutter RD, Tannenbaum M, Ultmann JE. Systemic mast cell disease. Ann Intern Med. 1963;59:887-906.
5. Kaye WA, Passero MA. Respiratory distress and hypoxemia in systemic mastocytosis. Chest. 1979;75:87-8.
6. Bayle JY, Arnouk H, de Perthuis D, Chouvet B, Germain-Pastene M, Cozon G, Béjui-Thivollet F, Pérol M, Sanson C, Guérin JC. Indolent mastocytosis and bronchial hyperreactivity. A case report. Rev Mal Respir. 1994;11:503-6.
7. Mochizuki H, Morikawa A, Kurosawa M. Bronchial hyperresponsiveness in a patient with systemic mastocytosis. Respirology. 2002;7:285-8.
8. Wardlaw AJ, Dunnette S, Gleich GJ, Collins JV, Kay AB. Eosinophils and mast cells in bronchoalveolar lavage in subjects with mild asthma: relationship to bronchial hyperreactivity. Am Rev Respir Dis. 1988;137:62-9.
9. Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. N Engl J Med. 2002;346:1699-705.
10. Mazzarella G, Grella E, Romano L, Perna A, Marzo C, Guarino C, Cammarata A, Bianco A, Liccardo G. Protective effects of nedocromil sodium on cellular and biohumoral components present in the bronchial alveolar lavage fluid and in peripheral blood in atopic asthmatics. Respiration. 1994;61:207-13.

Manuscript received April 14, 2009; accepted for publication, July 15, 2009.

Eusebi Chiner
Secció de Pneumologia
Hospital Universitari Sant Joan d'Alacant.
Ctra. Alacant-València s/n.
03550 Sant Joan d'Alacant, Spain
E-mail: chiner_eus@gva.es

Immunoglobulin E Reactivity to nOle e 1 as a Diagnostic Marker of Allergy to *Olea europaea* Pollen

MT Belver, J Jurado-Palomo, I Bobolea, MC López-Serrano, S Quirce
Hospital Universitario La Paz, Servicio de Alergia, Madrid, Spain, Bilbao, Spain

Key words: Olive pollen. Ole e 1. Major allergen. Component-resolved diagnosis.

Palabras clave: Polen de olivo. nOle e 1. Alérgeno principal. Diagnóstico por componentes.

Sensitization to *Olea europaea* pollen is common in patients living in Mediterranean countries. In Madrid, the most common allergenic pollens in patients with pollinosis are grass pollen, with a prevalence of positive skin prick test results of 94%, followed by olive pollen (61%) [1]. However, the clinical relevance of sensitization to olive pollen has been questioned since it could be due to cross-reactivity between this pollen and unrelated plant species [1]. Component-resolved diagnosis involves the use of marker allergens capable of differentiating between genuine sensitization of patients to a given allergen and cross-sensitization to several allergen sources [2]. In this regard, Ole e 1 has been proposed as a diagnostic marker for sensitization to *Oleaceae* species [3].

The objective of this study was to assess the clinical usefulness of specific immunoglobulin (Ig) E determination of nOle e 1 as a diagnostic marker of primary allergy to olive pollen in patients with pollinosis living in Madrid.

Patients older than 14 years who consulted our outpatient clinic for respiratory symptoms (rhinitis and/or asthma) during springtime were consecutively recruited throughout 2008. Skin prick tests were performed with a panel of common airborne allergens (ALK-Abelló, Madrid, Spain). Total serum IgE and specific IgE levels to olive pollen were measured in patients' sera by ImmunoCAP (Phadia, Uppsala, Sweden).

Fifty-three patients with a positive skin test and ImmunoCAP result for olive pollen (>0.70 kU/L) were included. Allergen-specific IgE (ImmunoCAP) to nOle e 1 was measured in all of them. Forty-nine (92.4%) of these patients also had a positive skin test to grass pollen. Of the 53 patients recruited, 30 were women (56.6%) and the mean age was 30 years. Twenty-nine (54.7%) had seasonal rhinoconjunctivitis and 24 (45.3%) had symptoms of rhinoconjunctivitis and asthma. In 49 patients (92.5%), IgE determination to nOle e 1 was positive (geometric mean [SD], 6.91 [3.01] kU/L). In the 29 patients with rhinoconjunctivitis, IgE levels to nOle e 1 were 5.21 (2.43) kU/L whereas in the 24 patients with rhinoconjunctivitis and asthma they were 9.78±6.05 kU/L (not significant, P=.098) (Figure). The IgE determination of nOle e 1 was negative in just 4 (7.5%) of the 53 patients with a positive skin test and ImmunoCAP result for olive pollen. This positivity may be due to cross-reactivity with unrelated pollens as 3 of the patients were sensitized to grass pollen and the fourth patient was sensitized to *Plantago lanceolata* [3,4].

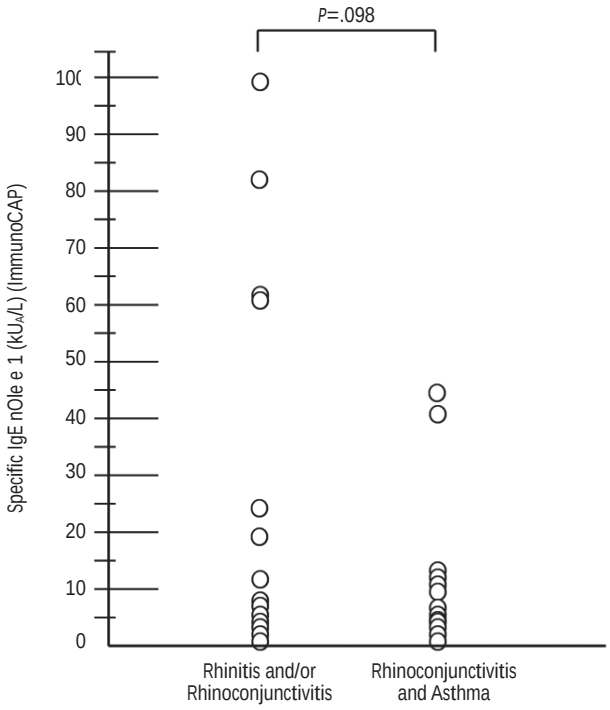

Figure. Specific immunoglobulin (Ig) E levels to nOle e1 in patients with rhinitis and/or rhinoconjunctivitis and in those with rhinoconjunctivitis and asthma.

In conclusion, these results demonstrate that the majority of patients living in Madrid who are sensitized to olive pollen show IgE reactivity to nOle e 1, confirming the importance of this allergen as a diagnostic marker of primary sensitization to olive pollen. Moreover, component-resolved diagnosis, involving the measurement of IgE reactivity to this purified olive pollen allergen, allowed us to rule out cross-reactivity with other allergens. Thus, we consider this simple diagnostic approach to be useful for the selection of patients and allergen extracts for allergen immunotherapy [2].

Although Ole e 1 has been found to significantly contribute to the total allergenicity of olive pollen extract and its concentration is closely related to the allergenic reactivity of the whole pollen extract [5,6], sensitization to other allergens can be clinically significant. Quiralte et al [7] reported that IgE-mediated sensitization to Ole e 2 and Ole e 10 showed a strong association with asthma, whereas no association was detected with Ole e 1, Ole e 3, Ole e 6, or Ole e 7 in the same population. Finally, Barber et al [4] recently described that IgE responses to the minor olive allergens Ole e 7 and Ole e 9 were markers of more severe allergic disease.

References

1. Subiza J, Jerez M, Jiménez JA, Narganes MJ, Cabrera M, Varela S, Subiza E. Allergenic pollen pollinosis in Madrid. J Allergy Clin Immunol. 1995;96:15-23.
2. Valenta R, Twaroch T, Swoboda I. Component-resolved diagnosis to optimize allergen-specific immunotherapy in the Mediterranean Area. J Investig Allergol Clin Immunol. 2007;17, Suppl. 1:88-92.
3. Palomares O, Swoboda I, Villalba M, Balic N, Spitzauer S, Rodriguez R, Valenta R. The major allergen of olive pollen Ole e 1 is a diagnostic marker for sensitization to Oleaceae. Int Arch Allergy Immunol. 2006;141:110-8.
4. Barber D, de la Torre F, Feo F, Florido F, Guardia P, Moreno C, Quiralte J, Lombardero M, Villalba M, Salcedo G, Rodríguez R. Understanding patient sensitization profiles in complex pollen areas: a molecular epidemiological study. Allergy. 2008;63:1550-8.
5. Lombardero M, Quirce S, Duffort O, Barber D, Carpizo J, Chamorro MJ, Lezaun A, Carreira J. Monoclonal antibodies against Olea europaea major allergen activity of affinity purified allergen and depleted extract and development of a radioimmunoassay for the quantitation of the allergen. J Allergy Clin Immunol. 1992;89:884-94.
6. Villalba M, Batanero E, López-Otín C, Sánchez LM, Monsalve RI, González de la Peña MA, Lahoz C, Rodríguez R. Amino acid sequence of Ole e 1, the major allergen from olive tree pollen (Olea europaea). Eur J Biochem. 1993;216:863-9.
7. Quiralte J, Llanes E, Barral P, Arias de Saavedra JM, Saenz de San Pedro B, Villalba M, Florido JF, Rodríguez R, Lahoz C, Cárdaba B. Ole e 2 and Ole e 10: new clinical aspects and genetic restrictions in olive pollen allergy. Allergy. 2005;60:360-5.

Manuscript received July 6, 2009; accepted for publication, August 17, 2009.

María Teresa Belver
Hospital Universitario La Paz
Servicio de Alergología
Paseo de la Castellana, 261
28046 Madrid, Spain
E-mail: mtbelver18@gmail.com