Wasp Venom Immunotherapy in a Patient With Immune-Mediated Inflammatory Central Nervous System Disease: Is it Safe?

Nittner-Marszalska M[1], Kowal A[2], Szewczyk P[3], Guranski K[4], Ejma M[4]

[1]*Department of Internal Diseases and Allergology, Wroclaw Medical University, Wroclaw, Poland*

[2]*Department of Pulmonology, Wroclaw Medical University, Wroclaw, Poland*

[3]*Department of Radiology, Wroclaw Medical University, Wroclaw, Poland*

[4]*Department of Neurology, Wroclaw Medical University, Wroclaw, Poland*

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Venom immunotherapy (VIT) is the only highly effective way of treating patients with hymenoptera venom allergy (HVA). The most serious anaphylactic symptoms of HVA (HVA-SYS IVo) are life-threatening, thus making their occurrence an unconditional recommendation for VIT. Yet, VIT is contraindicated in immune-mediated inflammatory diseases.

We present the case of a 55-year-old woman with autoinflammatory neurological disease (initially diagnosed with relapsing remitting multiple sclerosis) who received VIT following an anaphylactic reaction (SYS-IVo) to wasp sting (*Vespula germanica*). Allergy tests showed the presence of specific IgE antibodies to wasp venom (intradermal test at 0.001 µg/mL, 12×12 mm; sIgE class 2). The basal serum tryptase concentration was normal. Her past medical history included gastrointestinal reflux, mild gastritis, allergy to ketoprofen and metamizole sodium, and seronegative spondyloarthropathy. At the age of 50, she was diagnosed with remitting-relapsing multiple sclerosis. Her first symptoms of neurological damage were mild facial weakness, mild instability with the eyes closed in the Romberg test, and clumsy movements of the left hand. Magnetic resonance imaging (MRI) was performed twice and revealed multiple hyperintense areas that were considered demyelinating lesions. The cerebrospinal fluid study showed intrathecal production of immunoglobulins (Tibbling-Link IgG index, 1.75 [normal range, 0.2-0.85]). Visual evoked potentials were normal. Lyme disease was excluded. The patient was treated with intravenous methylprednisolone (Solu-Medrol, 1000 mg/d over 5 days) during 3 exacerbations of the disease. Progression in her disability was measured using the Kurtzke Expanded Disability Status Scale (EDSS). Her initial EDSS was 1.5, which rose to 4.0 after the last exacerbation of the disease.

The patient met the clinical and immunological criteria for VIT. Another reason in support of the decision to administer VIT was the patient's physical disability, which might have hindered attempts to avoid a sting, especially given that she lives in an area with high exposure to stinging insects. The decision to start VIT was made despite the hitherto accepted belief that autoimmunological diseases constitute a contraindication to immunotherapy. At the time the patient qualified for VIT, her condition was stable, with no new active neurological symptoms.

No complications were recorded during the induction phase (ultrarush; Pharmalgen, ALK-Abelló) and a complete 5-year course of VIT. There were no local or systemic allergic reactions. Neurological symptoms did not intensify, and no new symptoms appeared. The patient did not experience exacerbation of her neurological disease; the EDSS score remained unchanged. The findings in subsequent MRI examinations of the brain were stable, with no new lesions. The MRI revealed no lesions in the temporal lobes or posterior fossa structures and no juxtacortical lesions (Figure, A). However, numerous, small, irregular, hyperintense, and locally confluent lesions were observed in the FLAIR sequence. These were located in the white matter and showed a predilection for the subcortical area of the frontal and

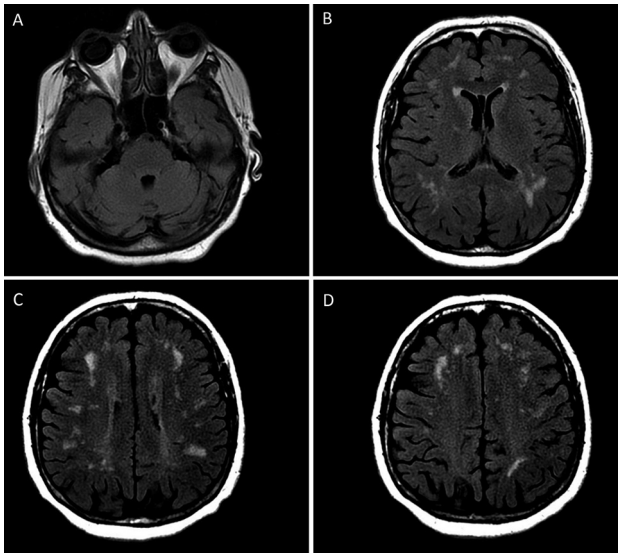

Figure. Magnetic resonance images.

parietal lobes (Figure, B, C, D); only a few periventricular lesions were visible in the right frontal and parietal lobes (Figure, B). All lesions were irregular and poorly demarcated. Administration of contrast medium did not reveal pathological enhancement of the lesions. The MRI scans of these changes did not meet the McDonald criteria for dissemination in time and space. The image and location of the lesions could suggest an underlying vascular mechanism, especially in the course of vasculitis. The immunological profile of the patient's serum was reassessed. Antinuclear antibodies alone were present; there were no other autoantibodies (anticardiolipin, cANCA, pANCA, SS-A/Ro, Ro-52, SS-B/La, Sm, Sm/RNP, Jo-1, Sci-70, PM-Sci, CENP B, PCNA, dsDNA, histone proteins, anti-P, AMA M2, or dsDNA-NcX IgG). The results of MR angiography of the head were normal. The patient was finally diagnosed with idiopathic primary central nervous system vasculitis. The diagnostic tests excluded the secondary origin of the condition. While VIT did not have a negative effect on the patient's neurological condition, the effectiveness of the therapy cannot be clinically assessed owing to the lack of a field sting. Indirectly, however, it may be endorsed by intradermal test results that are currently positive only at a venom concentration of 1 μg/mL.

Co-occurrence of an allergy and an immune-mediated inflammatory disease, autoimmune disease, and autoinflammatory disease (AID) is considered an absolute contraindication to allergen immunotherapy (AIT) by some guidelines [1] and a relative contraindication by others [2]. The contraindication results from a hypothetical fear of a negative effect of allergen stimulation on the activity of the inflammatory process and of disturbing TH_1/TH_2 balance of peripheral helper T cells. These concerns are theoretical, because there are no reliable clinical studies or even clinical observations that could confirm them. Actually, such studies would be difficult to carry out, since patients with AID are routinely disqualified from AIT according to existing recommendations.

However reasonable the contraindications in most patients receiving AIT, in the case of life-threatening HVA, the benefits of VIT exceed the risk of an exacerbation of AID, thus explaining why, when justified in patients with AID, VIT can be administered during a stable period of the disease. Of the few reports that describe such procedures, one refers to a patient with HVA and systemic lupus erythematosus who, as in the present case, underwent VIT uneventfully (ie, with no exacerbation of systemic lupus erythematosus) [3].

The lack of a negative interdependence between AIT and AID may also be supported by the fact that there are few reports of manifestations of AIDs during the course of AIT. Reports of vasculitis, scleroderma, Sjögren syndrome, rheumatoid arthritis, and multiple sclerosis during AIT are based on case reports [4-8], whereas the evidence that AIT may reduce the risk of the occurrence of autoimmune diseases is from observational studies. In a registry-based observational study, the incidence of AID was lower in allergic patients treated with AIT than in allergic patients given conventional pharmacotherapy [9]. Similar findings were reported by Bozek et al [10], whose long-term study revealed that the incidence of AID (including systemic vasculitis, multiple sclerosis, rheumatoid arthritis, ulcerative colitis, Crohn disease, Graves disease, scleroderma, and psoriasis) in patients treated with AIT is low and is in fact lower than in allergic patients treated symptomatically [10].

When we decided to administer VIT in the present cases, we were first and foremost concerned for the patient's safety during AIT and feared exacerbation of the neurological condition. However, we also considered the benefits of VIT. Given that neither of these complications occurred, it may be appropriate to recommend VIT in patients with HVA and AID.

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Konstanty Guranski
Department of Neurology
Wroclaw Medical University, Borowska 213
50-556 Wroclaw, Poland
E-mail: kguransk@interia.pl

Pseudomonas aeruginosa Liver Abscess as the First Manifestation of X-Linked Agammaglobulinemia With a Novel Mutation

Muñoz-Miguelsanz MA[1], Álvarez Morales T[2], Martín García JA[2], Martínez Gallo M[3], Santos Pérez JL[2]
[1]*Pediatric Surgery Department, Virgen de las Nieves Children's Hospital, Granada, Spain*
[2]*Pediatrics Department, Virgen de las Nieves Children's Hospital, Granada, Spain*
[3]*Immunology Department, Vall d'Hebron Hospital, Barcelona, Spain*

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Pyogenic liver abscesses are infrequent in children, occurring in 8-20 per 100 000 inpatients [1]. They originate in the intestine or biliary tract or less frequently through hematogenous spreading. The latter is more common in children with underlying diseases, such as primary immunodeficiency, and often with defective phagocytosis and severe cellular or humoral disorders.

Staphylococcus aureus is the most common cause of liver abscesses [2]. Data for other pathogens in children are limited, although 2%-6% of adult liver abscesses are caused by *Pseudomonas aeruginosa* [3].

We report the case of a pediatric patient with a *P aeruginosa* liver abscess that was managed medically and diagnosed as X-linked agammaglobulinemia (XLA) with a previously unreported mutation.

A 19-month-old boy with no significant past medical or family history presented with general malaise and high fever (peak, 40ºC). On examination, the patient was pale and irritable with mottled skin. Meningeal signs were absent, and the results of the abdominal examination were normal. The leukocyte count was 1.8×10^3/mm^3 (polymorphonuclear, 0.19×10^3/mm^3), and C-reactive protein was 413 mg/L. The patient was started on intravenous cefotaxime, which was switched to meropenem and amikacin after *P aeruginosa* grew in blood cultures. Urinary and cerebrospinal fluid culture results were normal, as were the chest x-ray and echocardiogram findings. A subsequent abdominal and soft tissue ultrasound showed a liver abscess measuring 24×15 mm in segment VI of the right lobe and 2 subcutaneous tumors with central necrosis in the right leg and pelvis (20×10 mm and 30×10 mm). Purulent fluid drained from both abscesses was positive for *P aeruginosa*. Given the patient's clinical condition and the size of the abscesses, surgery was delayed and medical management was continued.

Table. Blood Test Results

	Admission	3 Days M+A	11 Days M+A	3 Weeks M+A+F	Discharge 2 IV Doses of Ig
Leukocytes, $\times 10^3/\mu L$	1.8	27.3	8	6.4	9.1
Neutrophils, $\times 10^3/\mu L$	0.19		4.5	0.8	0.97
Lymphocytes, $\times 10^3/\mu L$	0.61	4.99	2.71	4.8	7.21
CRP, mg/dL	41.3	8.7		0.9	0.2
ALT, U/L			30	26	29
AST, U/L			19	18	17
GGT, U/L			48	32	21
LDH, U/L			317	228	241
Humoral Immunity					
C3, mg/dL			146		132
C4, mg/dL			50		32
IgA, mg/dL			67	44	33
IgG, mg/dL			544	550	1310
IgM, mg/dL			12	9	9
Lymphocyte Subsets					
NK/µL (%)			266.8 (8.5)	1436.5 (22.6)	1320 (18.1)
B lymphocytes/µL (%)			6.2 (0.23)	6.2 (0.1)	19.1 (0.3)
CD3 T lymphocytes/µL (%)			2849.7 (90.6)	4823.5 (76)	5919.3 (81)
CD4 T lymphocytes/µL (%)			1982.6 (63.1)	3318.2 (52.3)	3940.9 (54)
CD8 T lymphocytes/µL (%)			572.6 (18.2)	1136.2 (17.9)	1514.7 (20.7)
Total lymphocytes/µL			3144.2	6349.5	7304.3
Vaccine Antigens					
Antimeasles IgG			Positive		
Anti-HBsAb			Nondetectable		
Antirubella IgG			Nondetectable		
Oxidative index test			Normal		

Abbreviations: A, amikacin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; F, fluconazole; GGT, γ–glutamyltransferase; LDH, lactate dehydrogenase; M, meropenem.

Findings from clinical and blood tests improved (Table) and the liver abscess gradually decreased in size. After 3 weeks, *Candida parapsilosis* was isolated in the blood culture. Therapy was started with liposomal amphotericin B and then switched to intravenous fluconazole once the results of the antifungal susceptibility test were available.

Further investigations included immunological testing. Immunoglobulin levels were as follows: IgG, 544 mg/dL; IgA, 67 mg/dL; and IgM, 12 mg/dL. Lymphocyte phenotyping showed marked B lymphopenia (0.1%; 6/mm^3). The result of the neutrophil oxidative burst assay was normal. Serological tests for previous vaccines were negative for hepatitis B and rubella and positive for measles.

Given the absence of B cells despite normal immunoglobulin levels, genetic tests were performed to rule out primary immunodeficiency.

The Bruton tyrosine kinase (*Btk*) gene sequencing revealed a pathogenic hemizygous mutation (c. 1631 > 2 TA, exon 16 donor splice site).

Ultrasound confirmed the progressive decrease in the size of the liver abscess until complete disappearance after 1 month of antimicrobial and antifungal treatment. Serial blood cultures were negative for *P aeruginosa* and *Candida* species.

Therapy with intravenous immunoglobulins (0.5 g/kg) was started, and no new complicated infectious events were detected.

Liver abscesses are very uncommon in children. Classic symptoms such as fever, right upper quadrant pain, and jaundice are more common in adults than in children, who often present nonspecific symptoms, such as gastrointestinal symptoms, respiratory distress, and cutaneous rash. While etiology is varied, *P aeruginosa* is rare. Moore et al [4]

reported one of the largest series of liver abscesses in infancy (n=124). Most cases were pyogenic in origin, although none were caused by *P aeruginosa*.

No specific guidelines have been drafted for children. However, percutaneous drainage has been recommended in adults in the following cases: abscess size >5 cm; location on the left side (due to higher risk of rupture); absence of clinical improvement after 72 hours of antibiotic treatment; and increase in size or liver failure [5].

In the case series of Moore et al [4], the initial treatment was conservative. Percutaneous drainage was only performed after no measurable improvement following 24-48 hours of antibiotic treatment. The number of patients treated conservatively was 18/124, with complete resolution and minimal residual lesions at 3 weeks. In the case we report, the abscesses could not be seen on ultrasound after 4 weeks of antibiotic treatment.

A literature search revealed only 2 cases in children presenting with liver abscess caused by *P aeruginosa* [6,7]. In both patients (aged 19 and 36 months), treatment was with intravenous antibiotics and percutaneous drainage. In the first case, surgery was the initial approach. The second case was first managed conservatively. Since the abscess increased in size and new abscesses formed, a percutaneous drain was inserted. However, the patient died.

Severe, persistent or unusual infections in children suggest primary immunodeficiency. Although serum Ig levels were not significantly decreased, the B lymphocyte count was less than 2%, strongly suggesting XLA. The definitive diagnosis of XLA is made based on clinical criteria and the presence of the *Btk* gene mutation [8]. In the case we present, this mutation affected the second position of the exon 16 donor splice site, leading to nonfunctional incomplete protein production and failure of B lymphocyte maturation.

In XLA, the association between phenotype and genotype is controversial [9]. Mutations in *Btk* produce mRNA and protein alterations and, subsequently, impairment of B lymphocyte maturation. Using bioinformatics techniques, the potential consequences of mutations can be predicted and classified as *severe* or *less severe*. In the present case, the mutation affected splicing, leading to a truncated *Btk* protein. The consequences of the mutation were therefore considered severe. These mutations are associated with onset before 2 years in invasive infections (sepsis, central nervous system infections, and deep-seated infections) [10]. Less severe mutations have been described in patients with normal Ig levels. In the present case, the clinical course was severe despite the absence of significant hypogammaglobulinemia, which could be characteristic in this mutation. However, in some cases, there is no association between Ig levels at diagnosis and disease severity, suggesting that the severity of the mutation is a better predictor of clinical course. Therefore, therapy with intravenous immunoglobulins was started immediately, and no severe infections were subsequently detected.

We conclude that conservative management based on appropriate antibiotic therapy is a suitable option in liver abscess. Early recognition of conditions associated with primary immunodeficiency is important for diagnosis and successful long-term prognosis.

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Juan Luis Santos Pérez
Pediatrics Department
Virgen de las Nieves Children's Hospital
Avda. Fuerzas Armadas 2
18014 Granada, Spain
E-mail jlsantosperez@gmail.com

Frequency and Course of Eosinophilic Esophagitis During Oral Immunotherapy for Cow's Milk Allergy in a Series of 57 Children

Gómez Torrijos E[1], Mendez Díaz Y[1], Moreno Lozano L[1], Extremera Ortega AM[1], Borja Segade J[1], Feo Brito JF[1], Rodríguez Sánchez J[2], García Rodríguez R[1]

[1]*Allergy Department, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain*

[2]*Gastroenterology Department, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain*

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Numerous experiences with oral immunotherapy (OIT) for cow's milk (CM) allergy in children have been published in recent decades [1]. The procedure is not risk-free. Immediate reactions are common and while late complications are rare, they are more frequently reported with milk than with other foods [2-4]. Fifty-seven children have undergone OIT for CM allergy in our department and 3 of them were diagnosed with eosinophilic esophagitis (EoE).

The case of patient 1 has been previously described [5]. Patient 2 was referred to our allergy department because he had experienced an episode of mild anaphylaxis at 6 months of age when milk formula was introduced into his diet. Prick tests performed at the time showed positive results to CM and its proteins (α-lactoalbumin, β-lactoglobulin, and casein). Specific IgE was positive to CM (45.4 kU/L), casein (50.3 kU/L), and β-lactoglobulin (16 kU/L). At the age of 11 years he successfully underwent OIT with CM, and was able to tolerate 250 mL after a 3-month build-up phase. The following year, the daily doses of CM had to be reduced to 125 mL because of episodes of bronchospasm with the ingestion of each dose of milk. He also experienced anaphylaxis after eating sheep's cheese. After 3 years of a daily maintenance dose of 125 mL of CM, the patient began to experience progressive dysphagia to solids and choking. We started treatment with omeprazole 40 mg once daily and maintained regular intake of CM. Two months later we performed the first endoscopy with biopsies and identified 30 eosinophils per high power field (HPF) in the proximal, medial, and distal esophagus. The results met the criteria for EoE established in the 2011 consensus recommendations [4 6]. Four months after the first endoscopy, and having followed a CM-free diet, the patient underwent a second endoscopic biopsy, which revealed no eosinophils in the esophagus. These results confirmed the remission of the EoE. The patient has continued on a CM-free diet for the last 3 years but experienced an episode of anaphylaxis with trace amounts of CM.

Patient 3 is an 8-year-old boy with a history of respiratory infection–induced bronchial hyperresponsiveness and allergy to CM protein since childhood. He experienced an episode of mild anaphylaxis at 3 months of age when milk formula was introduced into his diet. Prick tests performed at the time showed positive results to CM and its proteins (α-lactoalbumin, β-lactoglobulin, and casein). Specific IgE was positive to CM (34.5 kU/L), casein (20.3 kU/L), α-lactoalbumin (21 kU/L), and β-lactoglobulin (16 kU/L). The patient subsequently followed a strict CM avoidance diet. At the age of 8 years, he successfully underwent OIT for CM allergy, and was able to tolerate 250 mL of CM after the build-up phase, which lasted 3 months. The following year, daily doses of CM had to be reduced to 125 mL because the boy experienced episodes of oral allergy syndrome after the ingestion of milk and dairy products. After 3 years of a daily maintenance dose of 125 mL of CM, he began to experience central chest pain after eating solid foods. He remained asymptomatic for a month after starting a CM-free diet. A new endoscopy with esophageal biopsies by sections (proximal, medial, and distal) identified at least 30 eosinophils/HPF. After 2 years on a CM-free diet, the patient was still asymptomatic and an endoscopy with biopsies showed no eosinophils.

All patients allergic to CM who underwent OIT in our clinic and developed EoE showed unfavorable progress and required a dose reduction of CM during the first year, despite tolerating 250 mL at the end of the build-up phase. As is common in patients with severe CM allergy, tolerance was only partially achieved. Failure to tolerate goat's or sheep's cheese or CM is not uncommon in patients after OIT for CM allergy [7] and confirms the high specificity of the desensitization procedure.

Proton pump inhibitors (PPIs) were prescribed after the diagnosis of EoE, as these drugs are considered the first-line treatment for this condition, before diet or topical steroids [8].

In patient 2, the first endoscopy was performed 2 months after PPI treatment was started. Although the patient was already asymptomatic, the histologic findings confirmed the diagnosis of EoE. A second endoscopy performed after 6 months of CM avoidance showed that the EoE was in remission. In this case, similarly to that of patient 1 [5], the period of food avoidance necessary for the resolution of EoE after OIT was longer than the 6 weeks established for diet-based treatments [9]. Besides, the 2 patients lost tolerance of CM within weeks or months of a CM-free diet and experienced anaphylactic episodes after the accidental ingestion of CM.

The prevalence of EoE in our patients (5.2%) is higher than that previously reported for other foods (2.7%) [10]. Although there is a risk of this late complication in patients undergoing food OIT, the potential benefits should be weighed against the risk of immediate, potentially severe reactions due to the accidental ingestion of food. After 5 years, the 3 patients have remained asymptomatic on a CM-free diet.

One limitation of this study is that an esophagoscopy was not performed in any of the the patients before starting OIT and EoE may therefore have been present before the desensitization procedure. The fact that avoidance of CM led to the resolution of the esophageal disease, however, makes it unlikely.

We have reported on several patients who developed EoE 3 years after OIT for CM allergy and achieved partial tolerance of CM during the maintenance phase. The favorable clinical and histologic remission after the withdrawal of CM from the patients' diets confirms that the bovine proteins were responsible for the EoE. Before starting OIT, clinicians should enquire about esophageal dysfunction symptoms. If present, EoE should be ruled out before initiation of therapy. Patients due to undergo OIT should also be warned of the risk of EoE and informed about its symptoms. In brief, the risk-benefit profile of OIT should be carefully evaluated for each patient.

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Elisa Gómez Torrijos
Hospital General de Ciudad Real. Allergy Section
c/Obispo R Torija S/N
13005 Ciudad Real, Spain
E-mail: egomezt.cr@gmail.com

Occupational Contact Dermatitis in Spain

Holguín-Gómez L[1], Sastre Domínguez J[2]
[1]*Alergología Clínica, Universidad de Antioquia, Colombia and Allergy Division, Fundación Jimenez Díaz*
[2]*Allergy Division, Fundación Jimenez Díaz, Universidad Autónoma de Madrid, Madrid, Spain*

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Palabras clave: Dermatitis de contacto ocupacional. España. Profesiones de alto riesgo.

Occupational contact dermatitis (OCD) is one of the most common work-related illnesses in developed countries, accounting for up to one-third of all occupational diseases. It is an inflammatory skin condition caused by contact with materials found in the workplace. The 3 types of OCD are irritant contact dermatitis, allergic contact dermatitis, and contact urticaria [1].

The annual incidence of OCD is thought to be between 11 and 86 cases per 100 000 workers worldwide, and between 5 and 19 cases per 10 000 workers per year in Europe. The occupations with the highest risk include hairdressing, baking and other food services, mechanics, painting, construction, footwear manufacturing, health care work, and poultry farm and manual labor [1]. A study conducted by Bordel-Gómez et al [2] in Spain reported a prevalence of 21.3% for OCD in patients evaluated due to suspected contact dermatitis. The most widely affected workers were metallurgists, construction workers, and hairdressers.

The main risk factor for the development of irritant OCD is a moist environment, frequent trauma, and contact with solvents and detergents [3]. Allergic OCD, on the other hand, requires a T-cell response. In the case of contact urticaria, an IgE mechanism is involved [4].

The aim of the study was to describe the characteristics and sensitization patterns of patients treated at a specialist clinic in Spain following referral for suspected occupational dermatosis.

Information from 118 consecutive patients seen at the occupational allergy clinic of Fundación Jiménez Díaz in Madrid, Spain between October 2013 and August 2016 was evaluated retrospectively by examining the records held at the clinic. The department provides care for a patient population residing in an area of Madrid and surrounding provinces totalling around 8 million inhabitants. Patients were referred mainly by mutual insurance companies.

The evaluation included a physical examination and a complete occupational history, including evaluation of safety data sheets. The criteria proposed by Mathias was used to aid clinicians in assessing for OCD [5].

Patch tests were performed using the T.R.U.E. 36 TEST set and additional Chemotechnique series (e.g., metals, hairdressing products, gums, dyes, epoxy resins) depending on the patients' clinical history. Test results were interpreted using the criteria of the International Contact Dermatitis Research Group.

A slightly higher proportion of women (54%) than men had OCD. The mean (SD) age of the patients was 38.6 (10.4) years. Of the 76 patients (64%) with positive patch tests, 39 (51%) were positive to more than 1 allergen. Atopy was present in 7.6% of patients. Exposure time before development of skin lesions was less than 1 year in 33% of patients, 1 to 5 years in 26%, 6 to 10 years in 8%, and more than 10 years in 9%. The exposure time was unknown in 23% of patients. The hands were the most frequently affected area; 73% of all patients had OCD of the hands, which was allergic in 51.6% of cases and irritant in 21.3%. The next most frequently affected areas were the arms and/or forearms (32.6%; 21.35% allergic and 11.2% irritant) and the face and/or neck (21.3%; 17.6% allergic). The chest and/or lower limbs and widespread involvement were present in 6.7% and 5.6% of cases, respectively.

The patch test results are summarized in Figure A. The most frequently positive allergens were metals (29.4%), including nickel, cobalt, copper, vanadium, palladium, gold thiosulfate, and chromium. The reaction was clinically irrelevant in 30% of cases. The next most frequently positive allergens were rubber additives (black rubber, thiuram mix, carba mix, and colofony) and hairdressing products. Combined, rubber additives and hairdressing products accounted for 14% of cases. Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) was positive in 9.8% of patients and epoxy resins in 8.4% (Figure A).

In hairdressers, the most common positive allergens were p-phenylenediamine (19.5%), metals, acrylates, and MCI/MI (14.6% each). In construction and handling of resins, the 2 major allergens were epoxies and carba mix, which were both positive in 30.8% of patients. For workers using cleaning products, the most common sensitizers were thiuram, MCI/MI, and nickel (30%, 20%, and 20%, respectively). In mechanics and the automotive industry and other occupations involving the use and/or maintenance of machines, the main allergens were epoxy resin (33.3%), formaldehyde, quaternium-15, metals, and colophony (16.7% each).

The definitive diagnosis was allergic contact dermatitis in 52.5% of patients and irritant dermatitis in 22.9%. Other diagnoses were chronic urticaria/angioedema (3.4% of cases), atopic dermatitis (1.7%), and other nonallergic skin diseases (19.5%). The occupations with the highest risk were related to hairdressing (26%), building and handling of resins (15%), cleaning (10%), mechanical tasks, use and maintenance of machinery and the automotive industry (8%), food services and handling (7%), and health care work and the pharmaceutical industry (5%) (Figure B).

The European Surveillance System on Contact Allergy (ESSCA) network identified 10 617 patients from 11 European countries with a diagnosis of OCD during the years 2002 to 2010 [6]. The occupations associated with the highest risk of OCD were "other personal service workers", where hair

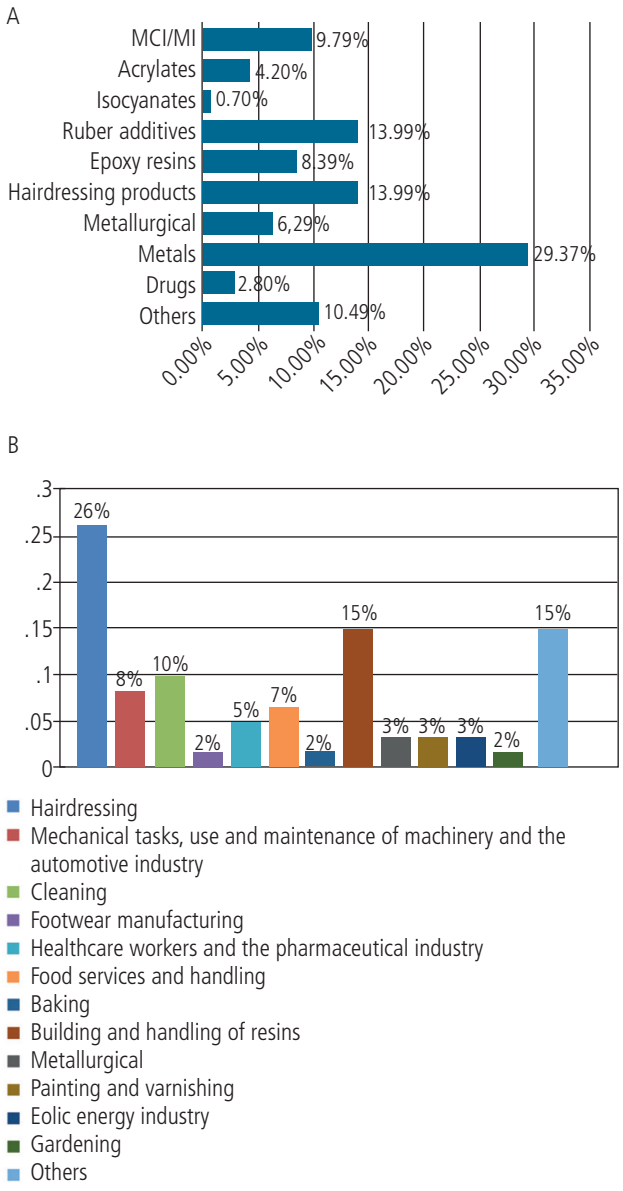

Figure. Sensitization profile (A) and type of activity (B) in allergic occupational contact dermatitis. MCI/MI indicates methylchloroisothiazolinone/methylisothiazolinone.

and beauty are a major component (17.4%) as well as those related to health (2.5%-17.9%) and metallurgy/ironworks (up to 12.9%). The most common allergens were thiuram (5.35%), MCI/MI (4.09%), and epoxy resins (3.42%). These findings coincide with those of Bensefa-Colas et al [7] in France in 2014 and Bauer in Germany in 2015 [8]. Apart from the previously described high-risk populations, our study also detected cleaning as a profession that is particularly vulnerable to OCD, coinciding with reports by Bauer [9] and Mirabilli et al in Spain [10]. We did not find OCD to be as frequent among health care workers as described by the ESSCA network [6]. Additionally, the trend toward a decreased prevalence of OCD in construction workers was confirmed [7,10].

The final diagnosis was allergic contact dermatitis in 53% of patients and irritant contact dermatitis in 23%, thus contrasting with the 2010 findings of the ESSCA, which reported that irritant OCD was more frequent [8]. This discrepancy may be due to bias in patient referrals in both studies.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Joaquin Sastre
Fundación Jiménez Diaz
Servicio de Alergología
Av. Reyes católicos 2
28040 Madrid, Spain
E-mail: jsastre@fjd.es

Delayed Allergic Reaction to Terbinafine With a Positive Lymphocyte Transformation Test

Gonzalez-Cavero L[1], Dominguez-Ortega J[1,3], Gonzalez-Muñoz M[2], Mayor-Ibarguren A[4], Tomás M[1], Fiandor A[1], Quirce S[1,3]
[1]*Department of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain*
[2]*Department of Immunology, Hospital La Paz, Madrid, Spain*
[3]*CIBER de Enfermedades Respiratorias, Ciberes, Madrid, Spain*
[4]*Department of Dermatology. Hospital La Paz, Madrid, Spain*

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Palabras clave: Terbinafina. Alergia. Reacción retardada. Test de transformación linfoblástica.

Terbinafine, a member of the allylamine class of antifungals, is one of the most commonly used drugs for the treatment of dermatophyte infections. Terbinafine exerts its pharmacological effect by inhibiting the early stage of the synthesis of ergosterol, a primary component of the fungal cell membrane; this causes ergosterol deficiency and accumulation of squalene, resulting in cell death [1]. Adverse reactions, most commonly mild gastrointestinal symptoms, are reported by approximately 10% of patients. Rarely, terbinafine may cause cutaneous adverse effects, such as rash, eczema, or pruritus, with an incidence of 2.7% [2]. The incidence of serious adverse effects is just 0.04% [3]. There have also been isolated reports of selective hypersensitivity reactions to this drug, including rare cases of erythema multiforme [3], Stevens-Johnson syndrome or toxic epidermal necrolysis [4,5], and acute generalized exanthematous pustulosis [6].

We present the case of a 34-year-old Bolivian woman with no significant personal history. In February 2016, she was prescribed oral terbinafine (Lamisil, Novartis Pharma) 250 mg/day and topical terbinafine (Lamisil tópico 1%, Novartis Pharma), 1 topical application over the infected area every 12 hours, for treatment of a *Trichophyton rubrum* infection affecting the gluteal area. Three days later, she experienced an episode of itchy skin in the area of application. A dermatologist evaluated the patient, recommended discontinuation of terbinafine therapy, and prescribed topical betamethasone and copper sulfate. However, the patient experienced worsening during the next 3 days, with development of progressive, coalescent, punctate, erythematous lesions spreading throughout the buttocks, groin, and thighs, with mild desquamation in some previously affected areas. There was no oral or mucosal involvement, and no pustular or vesicular lesions were observed. Eosinophilia was not present and no other organs or systems were involved. The patient reported no history of adverse reactions to any cosmetics, metal objects, or foods. She recovered completely after a 2-week course of oral prednisone and went on to complete itraconazole therapy for her fungal infection.

One month after the episode, a skin prick test with terbinafine (50 mg/mL) was performed and found to be negative. Patch tests with a standard T.R.U.E. TEST series (SmartPractice Denmark ApS) and terbinafine 1% in petrolatum [7] were also negative. In an attempt to clarify the underlying mechanism, 3 months after the reaction, we performed a lymphocyte transformation test (LTT) with terbinafine. Briefly, proliferation of lymphocytes from the allergic patient was measured as previously described [8]. Fresh peripheral-blood mononuclear cells separated over a density gradient (Histopaque-1077, Sigma-Aldrich) were incubated for 6 days at 10^6 cells/mL in triplicate with terbinafine (100 µg/mL-1 µg/mL). Phytohemagglutinin (5 µg/mL) was used as a positive control. Proliferation was determined by the addition of [^{3}H]thymidine (0.5 µCi/well) for the final 18 hours of the incubation period. Proliferative responses were calculated as stimulation indices (SI), defined as the ratio between the mean values of counts per minute in cultures with antigen and those obtained without antigen. A positive response, defined as an SI of over 2, was obtained with the drug. LTT with terbinafine in 3 different atopic and nonatopic controls showed no proliferative responses (Figure). As the patient refused to undergo any other in vivo tests, an oral challenge with the culprit drug was not performed.

We have reported on a patient who developed a delayed pruritic, punctate, and erythematous skin eruption after intake of terbinafine, with favorable response to discontinuation of the drug and systemic corticosteroid therapy. The clinical picture was consistent with symmetrical drug-related intertriginous and flexural exanthema (baboon syndrome) induced by terbinafine. The first administration of the drug in the gluteal area could have had some influence on the development of this clinical picture, but, unfortunately, a biopsy was not performed during the acute episode. The implication of terbinafine in the reaction was confirmed by a positive LTT. This diagnostic modality has been used previously to assess delayed allergic reactions [9,10]. It offers advantages over patch and intradermal tests, including absolute safety and the assessment of a T-cell response to the drug, especially when performed 3 to 9 months after the onset of the reaction.

To the best of our knowledge, this is the first reported case of hypersensitivity to terbinafine in which this drug was confirmed as the culprit by a positive LTT. The LTT could become a good diagnostic alternative for patients who experience delayed reactions to terbinafine.

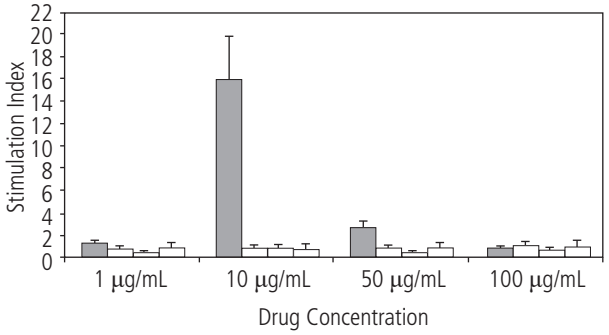

Figure. Lymphocyte transformation test results for different concentrations of terbinafine. Results are expressed as mean stimulation index of triplicate cultures. Error bars show SD. Solid fill and open bars represent the results from the patient and healthy controls (n=3), respectively.

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Lourdes Gonzalez-Cavero
Servicio de Alergia
Hospital Universitario La Paz
Paseo de la Castellana, 261
28046 Madrid, Spain
E-mail: lourdesgcavero@gmail.com

Steps Towards Clarifying the Clinical Relevance of Minor Olive Allergens in Areas With Extremely High Levels of Olive Pollen

Alcántara M[1], Sáenz de San Pedro B[1], Cañada C[1], Muñoz MA[1], Jimeno L[2], Villalba M[3], de la Torre F[2]

[1]*Allergology Unit of the Complejo Hospitalario de Jaén, Jaén, Spain*
[2]*ALK-Abelló, SA, Madrid, Spain*
[3]*Department of Biochemistry and Molecular Biology, Chemical Sciences Faculty, Universidad Complutense de Madrid, Madrid, Spain*

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Palabras clave: Diagnóstico por componentes. Enfermedad alérgica respiratoria. Perfiles de sensibilización alérgica. *Olea europaea*.

Sensitization patterns are highly influenced by allergen pressure, and in areas with sustained high pollen levels, minor allergens can behave as major allergens [1]. Olive pollen is a good example of this behavior. The prevalence of positive IgE results to minor allergens (Ole e 7 and/or Ole e 9) among patients allergic to olive pollen is almost 50%, with Ole e 7 being the primary sensitizer in specific individuals [1]. Furthermore, sensitivity to Ole e 7 has been associated with food anaphylaxis [2], although no cross-reactivity has been described between this allergen and food lipid transfer proteins (LTPs) [3]. In a recent study on the clinical role of olive pollen allergens, the authors hypothesized that Ole e 7 and 9 "seem to be markers of sensitization to panallergens, rather than specific pollen molecules" [4].

The aim of the present study was to determine the influence of allergen pressure on allergic sensitization profiles, the role of minor allergens, and the possible therapeutic implications in patients who are allergic to olive pollen recruited from an area of extreme olive pollen levels.

The study population comprised 100 consecutive patients recruited outside the olive pollination period. All participants had a history of allergic respiratory disease [5-6] by sensitization to olive tree pollen, positive skin prick test (SPT) results (mean wheal diameter, >3 mm) with olive pollen extract, and no previous allergy immunotherapy (AIT). They had all lived in the province of Jaen (Spain) for at least 5 years before their inclusion in the study.

This study was performed with the approval of the Research Ethics Committee of the Province of Jaen, and written informed consent was obtained from all participants.

ImmunoCAP (Thermo Fisher Scientific) was used to measure specific IgE (sIgE) reactivity to the following allergens: Ole e 1, 7, and 9; Phl p 1, 5, 7 (polcalcin), and 12 (profilin); Sal k 1; and Cup s 1.

Table. Sensitization Profiles of Study Patients With sIgE Negative to Ole e 1, Ole e 7, and Ole e 9

Patient	Ole e 1	Ole e 9	Ole e 7	Phl p 1	Phl p 5	Phl p 7	Phl p 12	Sal k 1	Cup s 1
1[a]	0.22	0	0	2.67	3.11	0	0	0.01	0.02
7	0	0	0	0.01	0	0	0	0.17	0.02
12[a]	0.05	0	0	15.9	0	0	0.01	11.3	0.01
13	0.02	0.01	0	1.96	0	0	0.01	0.01	0.02
16	0	0	0	1.35	3.73	0	0	0.03	0.02
20[a]	0.26	0	0	1.72	0.03	0	0.01	0.24	0.01
24[a]	0.11	0.09	0.03	>100	62.1	0.06	0.03	0.61	2.27
34	0	0.01	0.01	3.13	3.02	0	0.01	0.01	13.55
38	0	0	0	3.89	0.66	0	0	0.05	0.3
41	0.17	0	0	0	0	0	0	0.01	1.62
56	0.12	0	0.01	0	0	0	0.01	0	0
58[a]	0	0.01	0	0.1	0	0	0	0	0
59	0	0	0.01	0.02	0	0	1.35	0.01	0.49
79[a]	0.11	0	0.01	7.59	0	0	0.04	0.02	0
87[a]	0.19	0.01	0.15	0.04	0.01	0	0.02	0.03	0.02
88	0.16	0.01	0.01	0.01	0	0	1.91	0.02	0.02
91	0.07	0	0.01	1.1	2.27	1.02	0.02	0.78	0
93[a]	0.28	0.01	0.02	19.8	9.86	0.02	1.06	0.01	0.01
99	0.03	0	0.01	21.4	0	0	0.02	0.05	1.11
100[a]	0.25	0.01	0.01	0.02	0	0.01	0.01	0	0

[a]Patients in whom immunoblotting was performed.

The mean (SD) age of patients was 24.1 (13.4) years (range, 5-57 years), 52% were female, 72% were adolescents or adults, and 97% and 78% had allergic rhinitis and asthma, respectively.

The percentages of patients with positive sIgE ≥0.35 kU_A/L were as follows: Ole e 1, 73%; Ole e 7, 52%; Ole e 9, 34%; Phl p 1, 61%; Phl p 5, 27%; Phl p 7, 6%; Phl p 12, 17%; Sal k 1, 30%; and Cup s 1, 39%. The allergic *Olea* profiles were as follows: 25% of patients were sensitized to Ole e 1, 7, and 9; 21% were sensitized to Ole e 1 and 7; 8% were sensitized to Ole e 1 and 9; and 6% were monosensitized to Ole e 7. In 20% of cases, the patients showed negative sIgE to Ole e 1, 7, and 9.

The sensitization profiles of patients with negative sIgE to Ole e 1, 7, and 9 are shown in the Table. Immunoblotting was performed in 9 of the patients for whom sufficient serum was available to test whether the difference between SPT and sIgE results was due to different allergens or isoforms of these allergens. Immunodetection results showed that 6 patients were weakly positive for Ole e 1, while no signal was detected in 4 patients (data no shown). Some of these patients may be sensitive to other allergens not considered in this study.

The Ole e 1–positive/Ole e 7 and 9–negative profile was more frequent in nonasthmatics than in asthmatics (36.4% vs 14.1%, *P*=.0296), while asthmatic patients who showed a positive response to Ole e 1, 7, and 9 were more frequent than nonasthmatic patients with the same profile (29.5% vs 9.1%, *P*=.0056).

The prevalence of asthma was significantly higher in patients sensitized to Ole e 1 (OR, 2.9; 95%CI, 1.10-8.10; *P*=.0276), Ole e 7 (OR, 7.2; 95%CI, 2.22-23.33; *P*=.0003), Phl p 5 (OR, 4.7, 95%CI, 1.02-21.77; *P*=.0321), and Sal k 1 (OR, 5.6, 95%CI, 1.22-25.74 *P*=.0153). When the 4 allergens were analyzed together using a logistic regression model, only Ole e 7 and Phl p 5 retained a significant OR (4.98 [95%CI, 1.43-17.38] and 5.11 [95%CI, 1.00-26.10], respectively). However, when the analysis was carried out using a stepwise method, the only significant result was for Ole e 7 (OR, 7.2; 95%CI, 2.22-23.33).

The olive pollen count in Jaen can reach up to 20 000 grains/m^3, making it the region with the highest levels of olive tree pollen in Europe. In areas with low allergen pressure, Ole e 1 is the only marker of sensitization to olive [1], while in areas with high exposure, other allergens can be involved in the sensitization process.

In this study, no sIgE was detected against 3 olive pollen allergens in a large number of patients (20%). Consequently, diagnosis based on conventional techniques may be insufficient for these patients, even considering that 4 of them could have positive SPT by sensitization to profilin or polcalcin and that positivity to Sal k 1 may have led to a positive SPT and the similarity between Sal k 1 and Ole e 11 (pectin methyl esterases). Therefore, determination of sIgE to both major and minor allergens should be included in the diagnostic routine of these patients. In areas such as Jaen, minor allergens cause genuine allergic sensitization. The fact that there are patients who are monosensitized to Ole e 7 is an indication that this allergen can induce an allergic reaction by itself. An association between sensitization profiles and clinical profiles has been established for perennial allergens [7]; however, for seasonal allergens such as grass, this association is not as clear [8].

Also important is the possible indication of AIT in these patients. The standardization of allergen extracts is based, at best, on the quantification of the major allergen. In patients who are negative for Ole e 1, 7, and 9, standardization should take other allergens into account, as sensitivity to Ole e 7 is associated with a higher incidence of adverse reactions, as shown elsewhere [9]. Strict control of allergen content may be crucial for good tolerance. A recent publication examined the influence of sensitization to minor allergens on the post-AIT outcome with an *Olea* allergen extract [10].

In conclusion, in areas with extreme pollen counts, minor allergens can behave as genuine markers of allergic sensitization. Consequently, diagnosis should include determination of sIgE to these allergens in order to establish adequate immunotherapy.

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Fernando de la Torre
ALK-Abelló, S.A.
C/ Miguel Fleta, 19
28037 Madrid
E-mail: fernando.delatorremartinez@alk.net

Drug Eruption Caused by Rosuvastatin

Oda T, Sawada Y, Yamaguchi T, Ohmori S, Haruyama S, Yoshioka M, Okada E, Nakamura M
Department of Dermatology, University of Occupational and Environmental Health, Kitakyushu, Japan

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Palabras clave: Erupción medicamentosa. Rosuvastatina. Revisión de la literatura.

Hyperlipidemia causes progressive atherosclerosis through physical injury to the endothelial cells of arteries and it also exacerbates arteriosclerosis. The annual incidence of hyperlipidemia is increasing and treatment is necessary to improve cardiovascular events. Statins are a class of antihyperlipidemic drugs that inhibit hydroxymethylglutaryl-CoA (HMG-CoA) reductase, resulting in reduced low-density lipoprotein (LDL) cholesterol [1] and a lower incidence of coronary artery disease. Because of their strong antihyperlipidemic effects, various statin drugs are widely used for treatment. Rosuvastatin is one such drug with potent HMG-CoA reductase inhibitory activity [2]. Although other statin-induced drug eruptions have been reported, to our knowledge there have been no reports of cutaneous adverse events due to rosuvastatin in the English literature. We describe the first case of drug eruption caused by rosuvastatin and review similar cases reported for other statin drugs.

A 78-year-old woman noticed a small erythematous eruption on her extremities 1 month after the administration of rosuvastatin for hyperlipidemia. She gradually developed a generalized erythematous eruption and was referred to our department for evaluation. She had no history of drug hypersensitivity or other allergic diseases and reported no flu-like symptoms in recent years. Physical examination revealed small erythematous plaques and papules on her extremities (Figure A) and trunk; there was no mucosal involvement. A skin biopsy taken from an erythematous plaque revealed a lymphocytic and eosinophilic infiltration in the upper dermis (Figure B). Based on the clinical course, we speculated that the skin rash might be a drug eruption, possibly due to rosuvastatin. To investigate this suspicion, patch testing with rosuvastatin was performed and a positive reaction was observed at 48 hours for the 20% concentration. The skin eruption was diagnosed as a maculopapular-type drug eruption due to rosuvastatin. Two weeks after topical application of betamethasone butyrate propionate ointment and the discontinuation of rosuvastatin, the eruption improved.

We reviewed the literature and analyzed the clinical characteristics of our case and other statin-associated drug eruptions reported to date. To our knowledge, 32 cases, including ours, have been reported (Supplementary Table).

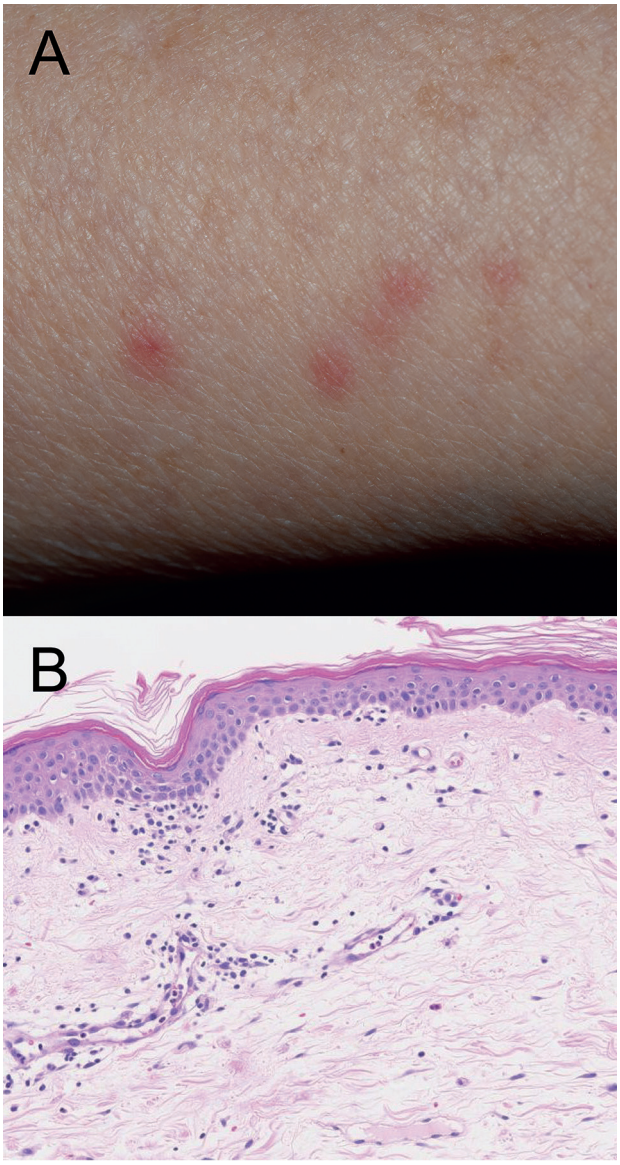

Figure. A, Small erythematous plaques and papules on the patient's right arm. B Histologic examination showing lymphocytic and eosinophilic infiltration in the upper dermis and around vessels.

The male to female ratio is 1.5:1, and the mean age is 63.8 years. The causative drugs were simvastatin (40.6% of cases), pitavastatin (31.3%), atorvastatin (18.8%), fluvastatin (6.3%), and lovastatin, pravastatin, and rosuvastatin (3.1% each). The most common eruption type was eczematous eruption. Interestingly, 31.3% of cases exhibited a lichenoid tissue reaction in the skin. Cross-reactivity is an important issue in the treatment of hyperlipidemia. One report described how a patient experienced photoallergy to simvastatin, a type 1 statin, but tolerated atorvastatin, a type 2 statin [3]. Another report described cross-reactivity between fluvastatin and rosuvastatin, both type 2 statins [4]. Cross-reactivity between different types of statins—atorvastatin (type 1) and simvastatin (type 2)—has also been reported [5].

We have reported the first case of drug eruption caused by rosuvastatin. Although the patient exhibited a relatively mild reaction, it should be kept in mind that rosuvastatin could cause severe cutaneous adverse events, similar to those reported for other statin agents. Further investigation is necessary to clarify the characteristics of rosuvastatin-induced drug eruption.

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Conflicts of Interest

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Yu Sawada
Department of Dermatology
University of Occupational and Environmental Health
1-1 Iseigaoka, Yahatanishi-ku
Kitakyushu 807-8555, Japan
E-mail: long-ago@med.uoeh-u.ac.jp

Anisakis Sensitivity in Italian Children: A Prospective Study

Tripodi S[1], Pingitore G[2], Calvani M[3], Scala G[4], Rodriguez-Perez R[5], Sfika I[1], Asero R[6]

[1]*Pediatric Department and Pediatric Allergology Unit, Sandro Pertini Hospital, Rome, Italy*

[2]*Allergy Unit, Grassi Hospital, Rome, Italy*

[3]*Pediatric Unit, S. Camillo Forlanini Hospital, Rome, Italy*

[4]*U.O.S.D. Allergologia e Immunologia Clinica, Loreto Crispi Hospital, Naples, Italy*

[5]*Hospital La Paz Institute for Health Research, IdiPAZ, Madrid, Spain*

[6]*Allergy Unit, Clinica san Carlo, Paderno Dugnano, Italy*

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Palabras clave: Alergia alimentaria. Niños. Alergia a pescado. *Anisakis simplex.*

Ingestion of live larvae (larval stage 3) of the nematode *Anisakis* simplex in raw or undercooked seafood that has not been deep-frozen may lead to gastrointestinal infection, and, in genetically predisposed individuals, sensitization to the helminth's proteins [1]. In Italy, sensitization to *Anisakis* is mostly associated with ingestion of traditional marinated or poorly cooked fish [2], although it is sometimes detected in individuals with no apparent risk factors. The prevalence of sensitization and allergy to *Anisakis* in children living in endemic areas is unknown. We investigated a cohort of children living in areas of Italy where hypersensitivity to *Anisakis* is endemic [2].

We studied 443 consecutive children (boys/girls, 258/160; mean age, 9.3 years; range, 1-17 years) presenting at 3 pediatric allergy centers in Rome and 1 center in Naples. A questionnaire was completed for all patients to detect possible risk factors for sensitization to *Anisakis* before the visit. All of the patients underwent skin prick testing (SPT) with a commercial extract of *A simplex* (2 mg protein/mL; ALK-Abelló) and with commercial extracts of house dust mites, codfish, shrimp, and cockroach (ALK-Abelló). In view of the well-known cross-reactivity between helminths, crustaceans, insects, and house dust mites [3], we only studied patients with unequivocal skin reactivity to *Anisakis* extract in the absence of any skin reactivity to house dust mite, shrimp, or cockroach in order to detect those who were genuinely sensitized to the helminth. Specific IgE to whole *A simplex* extract was measured using ImmunoCAP (Thermo Fisher Scientific). Furthermore, IgE to available recombinant *Anisakis* allergens (Ani s 1, Ani s 5, Ani s 9, and Ani s 10) was detected using ELISA [4-7]. Immunoblot analysis with whole *Anisakis* extract was also performed, as previously described [7]. In keeping with a previous study from Italy [2], *A simplex* allergy was considered to be highly likely in the presence of a history of 1 or more allergic reactions that unequivocally followed the ingestion of fish and a positive SPT result to *Anisakis* and negative SPT result to fish. Patients with a positive SPT result to *Anisakis* but no clinical history of fish-induced reactions were considered to be sensitized but not allergic to the helminth.

In all, 20 children (boys/girls, 13/8; mean age, 10.9 years; range, 5-16 years) corresponding to approximately 4.5% of the study population were eventually considered to be genuinely sensitized to *Anisakis* (Table). Apart from a significantly older mean age ($P<.02$), reactors did not differ from the control population in terms of prevalence of personal or familial consumption of raw, marinated, or undercooked fish, frequency of fishing as a hobby, or being in rooms where fish dishes were prepared. No *Anisakis*-sensitized child had a history of urticaria or gastroenteritis following ingestion of fish, and in no case did parents suspect that their son/daughter had fish allergy, although episodes of abdominal pain during the previous 2 years were reported by the parents of 3 children. Interestingly, 6 of 18 sensitized children (33%) had an aquarium at home, where fish and/or water turtles were bred. Since these data are not available for the general population, we do not know whether this represents a risk factor for sensitization to *Anisakis*.

The result of ImmunoCAP was positive in 11 cases, although specific IgE levels were often low. With ELISA, only 2 patients reacted to Ani s 1, 1 to Ani s 5, and 1 to Ani s 10, whereas no patients experienced hypersensitivity to Ani s 9. Immunoblot analysis revealed that sera from only 3 patients were positive and that all 3 showed IgE reactivity to a variable number of *Anisakis* proteins with a molecular weight ranging between 9 kDa and 170 kDa. The serum from 1 additional patient showed weak reactivity at 25 kDa only.

This is the first study specifically designed to assess the frequency of sensitization to *Anisakis* in children living in endemic areas. More than 4.5% of the children were genuinely sensitized to the parasite. Notably, this proportion is identical to that found in a larger study carried out in Italian adults [2] and suggests that sensitization to the parasite in endemic areas may occur at very young ages. Interestingly, *Anisakis*-sensitized children were significantly older than control children (the youngest was nearly 6 years old), suggesting that that the likelihood of sensitization increases over time and is most likely associated with a change in eating habits. However, none of the patients reported a history of urticaria or abdominal pain following ingestion of raw or marinated fish; this finding is in keeping with the fact that sensitization in this age group was mostly slight, as shown by the very low specific IgE levels recorded. The few children showing stronger sensitization reacted to defined major and minor *Anisakis* allergens such as Ani s 1, Ani s 5, and Ani s 10, although immunoblot analysis demonstrated IgE reactivity to other proteins as well. Of course, marinated and raw fish remain the most likely source of sensitization to the parasite in these children [2], although some sensitized children did not seem to have specific risk factors. Interestingly, 6 children had an aquarium at home where fish and/or turtles were bred; since sea fish–derived products and larvae are generally used to feed both freshwater and seawater fish, sensitization may sometimes occur via the

Table. Physical and Immunological Features of Anisakis-Sensitive Children

					ELISA (OD450)				
No.	Sex	Age, y	Wheal Size, mm	CAP, kU_A/mL	Ani s 1	Ani s 5	Ani s 9	Ani s 10	Immunoblot IgE, kDa
1	M	14.3	3	Neg	Neg	Neg	Neg	Neg	
2	M	13.9	6	Neg	Neg	Neg	Neg	Neg	
3	M	11.4	9	0.18	Neg	Neg	Neg	Neg	25
4	M	11.3	5	Neg	Neg	Neg	Neg	Neg	
5	M	11.6	6.5	12.1	0.24	Neg	Neg	0.1235	10, 26, 30, 38, 116
6	M	12.2	6	0.26	Neg	Neg	Neg	Neg	
7	M	10.8	5	Neg	Neg	Neg	Neg	Neg	
8	F	7.6	5	Neg	Neg	Neg	Neg	Neg	
9	F	9.2	5	Neg	Neg	Neg	Neg	Neg	
10	F	8.42	4	0.13	Neg	Neg	Neg	Neg	
11	F	10.3	3.9	0.57	Neg	Neg	Neg	Neg	
12	F	11.9	5	0.15	Neg	Neg	Neg	Neg	
13	F	13.9	6	0.1	Neg	Neg	Neg	Neg	
14	M	9	6	2.82	Neg	Neg	Neg	Neg	20, 25, 50, 170
15	M	5.75	4	Neg	Neg	Neg	Neg	Neg	
16	M	9.6	4.5	0.1	Neg	Neg	Neg	Neg	
17	F	7	3.6	Neg	Neg	Neg	Neg	Neg	
18	M	11	5	Neg	Neg	Neg	Neg	Neg	
19	M	16	7	14.3	0.4885	0.2235	Neg	Neg	9, 12, 30, 36, 38, 110
20	M	14	5	1.05	Neg	Neg	Neg	Neg	

respiratory tract or through the skin by handling such materials, although further studies are needed to confirm this hypothesis.

In conclusion, this study shows that sensitization to *Anisakis* in endemic areas is equally frequent in children and in adults. Pediatricians living in such areas should bear this in mind when evaluating young patients with acute gastroenterological or skin symptoms Risk factors other than ingestion of marinated fish could be involved in sensitization to *Anisakis*.

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Riccardo Asero
Ambulatorio di Allergologia, Clinica San Carlo
Via Ospedale 21, 20037 Paderno Dugnao (MI), Italy
E-mail: r.asero@libero.it

Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) Syndrome in Children: A Case Report

Mattoussi N, Ben Mansour A, Essadam L, Guedri R, Fitouri Z, Ben Becher S

Université de Tunis El Manar, Faculty of Medicine and Pediatrics Department, Bechir Hamza Children's Hospital, Tunis, Tunisia

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Palabras clave: Síndrome DRESS. RegiSCAR. Vancomicina. Niño.

Adverse drug reactions affecting the skin are common. Cutaneous hypersensitivity reactions range in severity, from mild reactions to severe cutaneous adverse reactions (SCARs). Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a distinct SCAR characterized by a potentially life-threatening hypersensitivity reaction with extensive rash, eosinophilia, and internal organ involvement occurring most commonly 2-6 weeks after initiation of medication [1]. In children, DRESS syndrome is rare and probably underdiagnosed [2]. Here, we report a rare case of DRESS syndrome induced by vancomycin in a 14-year-old boy.

The patient had sickle cell thalassemia (Sß) and was admitted to our clinic with fever and upper left quadrant pain. Laboratory findings showed leukocytosis (26 050/mm³), neutrophilia, and elevated C-reactive protein (209 mg/L). Abdominal ultrasound revealed heterogeneous splenomegaly indicative of onset of a microabscess or an extended splenic infarction. The patient was treated with hydration, paracetamol, cefotaxime (200 mg/kg/d), and vancomycin (60 mg/kg/d). The fever remitted after 4 days of antibiotics, and inflammation gradually resolved.

On day 13 of therapy with the 2 antibiotics, the patient presented again with fever (39°C-40°C), odynophagia, and diffuse lymphadenopathy in the cervical, axillar, and inguinal areas. The cervical nodes were voluminous (up to 4 cm in diameter) and tender. Four days later, he presented poor general status, periorbital edema, and pruritic maculopapular rash located initially on the face and trunk before becoming generalized. Laboratory tests revealed a white blood cell count of 27 100/mm³ with very high counts for lymphocytes (7300/mm³), mononuclear cells (1600/mm³), and eosinophils (5800/mm³), as well as hepatic cytolysis (AST, 341 IU/L; ALT, 313 IU/L) and hypergammaglobulinemia (29.4 g/L). The patient was diagnosed with DRESS syndrome, therapy with vancomycin and cefotaxime was stopped, and cetirizine was prescribed. As there was no pulmonary, cardiac, or renal involvement and the hepatic disorder was mild, we chose to maintain the antihistamine with no other medication and to monitor our patient.

Concomitant serology testing for HHV-6 revealed IgM and IgG antibodies, thus indicating a reactivation.

The patient improved progressively with resolution of fever, desquamation, regression of lymphadenopathy, and normalization of hepatic enzymes. After 6 months, patch testing with vancomycin and cefotaxime was positive for vancomycin and negative for cefotaxime. Oral challenge testing with cefuroxime was well tolerated. We used cefuroxime to carry out an oral challenge test because of side chain homology at position C3 between cefotaxime and cefuroxime and therefore possible cross-reactivity between the 2 drugs [3]. The patient was sent an allergy card for vancomycin.

Mild adverse cutaneous reactions to drugs are common and have multiple clinical features. Such reactions affect up to 2%-3% of all hospitalized patients [1]. DRESS syndrome is characterized by a potentially life-threatening hypersensitivity reaction with extensive rash, fever, and internal organ involvement (liver and kidney) occurring most commonly 2-6 weeks after initiation of a medication. The incidence of this syndrome is estimated to range from 1 in 1000 to 1 in 10 000 drug exposures [1]. Since the mortality rate of DRESS syndrome can reach 10%, it is very important to recognize this syndrome and manage it as soon as possible [2].

The diagnosis of DRESS is mainly clinical [4]. The syndrome typically begins with prodromal symptoms of pruritus and fever (38°C to 40°C). After several days, a descending pruritic maculopapular rash appears and may progress to erythroderma involving almost the entire surface of the skin [5]. The liver is the most frequently affected organ in DRESS syndrome (more than 70% of cases). Involvement ranges from a transient increase in liver enzymes to liver necrosis with fulminant hepatic failure [6]. Reactivation of HHV-6 has been shown to cause liver failure [1]. Consistent with these data, the patient we report on presented significant cytolysis with concomitant presence of anti–HHV-6 IgM, suggesting that hepatitis may be secondary to reactivation of HHV-6 [7].

Although the etiology of DRESS is poorly understood, genetic susceptibility markers have been identified within the HLA complex. According to Fernando [7], modification of host antigens by haptens (drugs or their metabolites) or noncovalent drug binding to endogenous proteins (the p-i concept) may drive proinflammatory immune responses. The concomitant detection of herpes virus and the recent demonstration of Epstein-Barr virus–specific immune responses in DRESS patients has also been considered a viral trigger of DRESS.

The most frequently implicated drugs in DRESS syndrome are aromatic anticonvulsants, allopurinol, and sulfamids [1,5]. However the list of potential causative agents is growing and now includes antiviral, biologic, and nonsteroidal anti-inflammatory, antimicrobial drugs [1,2]. A recent study of DRESS syndrome among inpatients at Massachusetts General Hospital found that vancomycin was involved in 5 of 6 cases identified over 18 months. The authors conclude that the causative agents of DRESS syndrome in an inpatient setting likely differ from those seen in the general population and point to the importance of recognizing vancomycin as a common cause of inpatient DRESS syndrome [8].

There are relatively few articles on DRESS syndrome in children [1]. The rare pediatric reports of vancomycin-induced DRESS syndrome describe a life-threatening condition with

Table. Investigational Findings Before Starting Vancomycin, After 3 Weeks of Vancomycin, and After Discontinuation of Vancomycin

Investigations	Before Starting Vancomycin	At 3 Wk of Vancomycin	After Discontinuation of Vancomycin
Hemoglobin, %	6.9	7.2	8
Total leukocyte count, cells/mm³	26 050	27 100	11 700
Lymphocytes/mm³	11 000	7300	6300
Eosinophils/mm³	400	5800	700
Atypical lymphocytes	0	6%	1%
Platelets/mm³	178 000	240 000	250 000
Urea, mmol/dL	5	1,91	2
Creatinine, µmol/dL	30	20	20
Alanine aminotransferase	72	353	88
Aspartate aminotransferase	32	341	56
Total bilirubin	24	20	18
Alkaline phosphatase	30	25	28
Antinuclear antibody	Negative	Negative	Negative
Patch test results		 Patch test to vancomycin: positive reaction	Patch test to vancomycin: positive reaction

acute liver failure, aggravated encephalopathy, and azotemia necessitating liver transplantation in one case and frank and refractory shock in another case [9].

It is clear that the patient in the present study developed DRESS syndrome fulfilling all of the inclusion criteria of the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) Study Group and Japanese Consensus Group (Table) [6].

The benign outcome of vancomycin-induced DRESS syndrome in the present patient confirms the broad spectrum of presentation of this syndrome in children and highlights that prompt withdrawal of the culprit drug is the main step toward complete recovery. Awareness of this drug reaction by pediatricians is crucial in order to avoid delayed diagnosis and poor outcome and to ensure long-term follow up of patients, since autoimmune disease can develop several months to years after clinical resolution of DRESS syndrome [10].

DRESS syndrome should be monitored systematically in patients receiving antibiotics, especially vancomycin. Withdrawal of the culprit drug should be discussed at the onset of rash, even before onset of systemic involvement, and before elimination of other possible diagnoses (eg, viral infection, autoimmune disorder, primitive or secondary hypereosinophilia syndrome, and pseudolymphoma). Further reports are needed to determine the incidence of DRESS syndrome in children and the extent to which antibiotics are involved in this syndrome in the pediatric population.

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Nadia Mattoussi
Bechir Hamza Hospital
1029, Av Bab Saâdoun
Tunis, Tunisia
E-mail: mattoussi.nadia@gmail.com

Total and Honeybee Venom–Specific Serum IgG4 and IgE in Beekeepers

Carballo I[1], Carballada F[2], Nuñez-Orjales R[2], Martín-Lázaro J[2], Vidal C[3], Gonzalez-Quintela A[1]
[1]*Department of Internal Medicine, Hospital and University of Santiago de Compostela, Santiago de Compostela, Spain*
[2]*Department of Allergy, Lucus Augusti Hospital, Lugo, Spain*
[3]*Department of Allergy, Hospital and University of Santiago de Compostela, Santiago de Compostela, Spain*

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The function of the fourth subclass of immunoglobulin G (IgG4) is not completely understood. Circulating IgG4 molecules can be asymmetric, ie, the 2 antigen-binding sites in IgG4 molecules may be different, resulting in bispecificity [1]. In allergic disorders, IgG4 can block the stimulation of mast cells by competing for allergen with membrane-bound IgE [1]. The development of allergen-specific IgG4 (sIgG4), whether spontaneously or after allergen immunotherapy, indicates the activation of tolerance-inducing mechanisms [1]. Thus, the determination of sIgG4 may be useful for assessing the efficacy of immunotherapy [1]. In addition to determination of sIgG4, measurement of total serum IgG4 has become clinically relevant, because high serum IgG4 concentrations are a diagnostic criterion for IgG4-related disease [2]. IgG4-related disease is a new concept that integrates many old diseases characterized by inflammation and fibrosis of 1 or more organs accompanied by a lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells [2]. Intriguingly, IgG4-related disease is related to allergic disorders [2].

Beekeepers are a suitable population for investigating serum IgG4 responses [3-5], since they are heavily exposed to stings and are therefore at high risk for developing honeybee venom (HBV) anaphylaxis. However, only a limited percentage of beekeepers develop severe anaphylaxis, because multiple stings act as natural immunotherapy, by increasing HBV-specific IgG4 (HBV-sIgG4) in serum [3-5]. To the best of our knowledge, the contribution of HBV-sIgG4 to total IgG4 has not yet been studied in individuals who are heavily exposed to HBV. Moreover, data on HBV-sIgG4 in general populations are lacking. This study sought to investigate total and HBV-specific serum IgG4 in beekeepers and controls. IgG4 concentrations were compared with those of total and HBV-specific serum IgE.

The study took advantage of a survey of beekeepers [6] conducted in northwest Spain (n=158, 81% men, median age 57 years, range 23-88 years). All participants completed a physician-administered structured questionnaire to determine beekeeping activities, sting episodes, and reactions to stings.

Reactions to the last recorded sting were classified as none, small local (<10 cm), large local (≥10 cm, typically lasting >24 hours), or systemic. Individuals drawn from the general adult population in the same area (n=465, 44% men, median age 54 years, range 18-92 years) [7] were used as controls. Fifty-four percent of beekeepers and 75% of controls lived in a rural environment. Total serum IgG4 was measured based on turbidimetry in a SPAPLUS analyzer (Binding Site Limited). Total serum IgE was assayed using the IMMULITE 2000 system (Siemens). HBV-sIgE and HBV-sIgG4 were assayed using the ImmunoCAP-250 system (Phadia). Total IgG4, total IgE, and HBV-sIgE concentrations in controls were reported elsewhere [7-9], as were total IgE, HBV-sIgE, and HBV-sIgG4 in beekeepers [6]. The analysis was performed using nonparametric approaches (Mann-Whitney test, Spearman rank correlation, and Jonckheere-Terpstra test for trend). The study was reviewed and approved by the regional ethics committee.

Serum concentrations of total and HBV-specific IgG4 and IgE in beekeepers (stratified by type of reaction to the last recorded sting) and controls are depicted in the Figure. HBV-sIgG4 concentrations were higher in beekeepers (median [IQR], 3.06 [0.81-3.6] mg/L; absolute range, 0.02-30.0 mg/L) than in controls (median 0.07 [0.03-0.17] mg/L; absolute range, 0-13.8 mg/L; *P*<.001). Among beekeepers, HBV-sIgG4 concentrations were highest among those who reported no reaction to stings. In general, the more severe the reaction to the sting, the lower the concentration of HBV-sIgG4 (Figure). The concentration of HBV-sIgG4 in beekeepers was positively correlated with the number of years beekeeping (rho, 0.365;

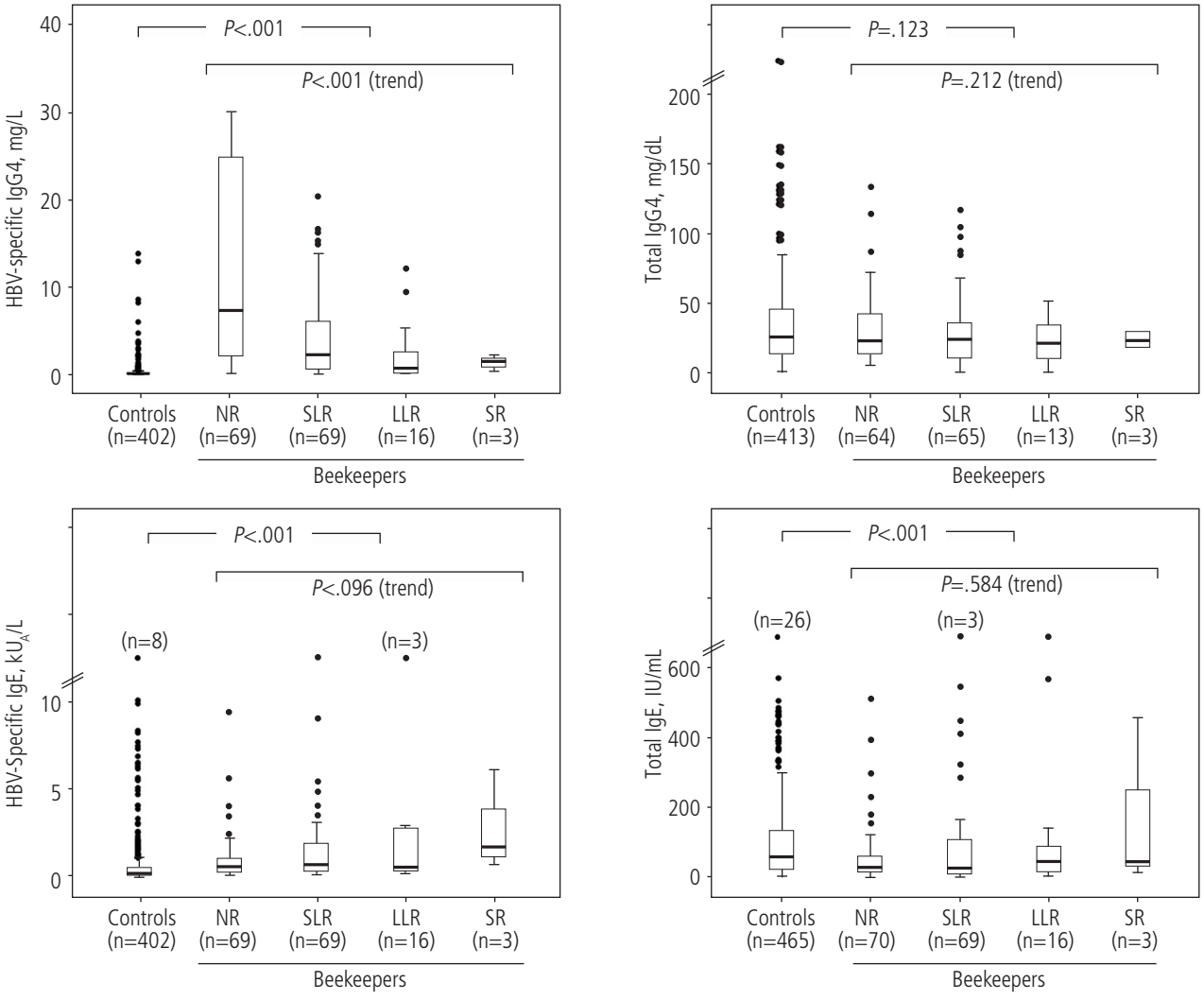

Figure. Serum concentrations of honeybee venom (HBV)–specific IgG4, HBV-specific IgE, total IgG4, and total IgE in controls and in beekeepers, stratified by reactions to the last recorded sting. Note that total IgG4 values were not available for 13 beekeepers and 52 controls; HBV-specific IgG4 values were not available for 1 beekeeper and 63 controls; HBV-specific IgE values were not available for 8 controls. LLR indicates large local reaction; NR, no reaction; SLR, small local reaction; SR, systemic reaction.

P=.014), number of beehives (rho, 0.485; *P*<.001), average number of bee stings per year (rho, 0.365, *P*<.001), and number of bee stings during the previous year (rho, 0.506; *P*<.001). These indicators of exposure to HBV were not correlated with HBV-sIgE, total IgE, or total IgG4 (data not shown). A correlation was recorded between HBV-sIgG4 and total IgG4 in beekeepers (rho, 0.245; *P*=.003) and controls alike (rho, 0.528, *P*<.001). The estimated proportion of total HBV-sIgG4 over total IgG4 was higher in beekeepers than in controls (median, 1.5% [range, 0%-30%] vs median, 0.03% [range, 0%-5%] respectively, *P*<.001). However, total IgG4 did not differ significantly between beekeepers and controls and was not associated with severity of reaction to stings (Figure). The concentration of HBV-sIgE was higher in beekeepers than in controls but was not significantly correlated with the severity of the sting reaction, although HBV-sIgE tended to be higher in beekeepers with more severe reactions (Figure). Total serum IgE was lower in beekeepers than in controls (Figure). The proportion of atopic individuals (ie, those with a positive skin prick test results to a panel of common aeroallergens in the area) was 22% in beekeepers and 26% in controls [6,7]. The negative association between beekeeping and lower IgE concentrations was independent of both age and atopic status (data not shown).

The results presented here are consistent with a tolerogenic role of HBV-sIgG4, namely, high concentrations of HBV-sIgG4 were associated with less severe sting reactions in beekeepers. Conversely, high concentrations of HBV-sIgE tended to be associated with a greater severity of sting reactions. These results generally confirm those of previous studies [3-5,10]. Intriguingly, total serum IgE was lower in beekeepers than in controls. Serum concentrations of HBV-sIgG4 and HBV-sIgE were higher in beekeepers than in controls. Of note, a sizeable proportion of control individuals had detectable low concentrations of HBV-sIgG4. This finding may be important, because previous studies on HBV-sIgG4 included few controls [4,5] and, to the best of our knowledge, no previous studies have investigated HBV-sIgG4 concentrations in the general population.

Total serum IgG4 concentrations did not differ significantly between beekeepers and controls. Serum concentrations of HBV-sIgG4 were correlated with those of total IgG4 in both beekeepers and controls. The contribution of HBV-sIgG4 to total IgG4 was higher in beekeepers than in controls, but the proportion of HBV-sIgG4 in relation to total IgG4 was small in both groups. Accordingly, beekeeping activities do not affect the clinical interpretation of total IgG4 concentrations.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Arturo Gonzalez-Quintela
Department of Internal Medicine
Hospital Clínico Universitario
15706 Santiago de Compostela, Spain
E-mail: arturo.gonzalez.quintela@usc.es

Eosinophilic Cellulitis Possibly Due to Mosquito Bite With High IL-5 Production

Mashima E, Sawada Y, Yamaguchi T, Ohmori S, Haruyama S, Yoshioka M, Okada E, Nakamura M
Department of Dermatology, University of Occupational and Environmental Health, Kitakyushu, Japan

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Eosinophilic cellulitis is a rare hypereosinophilic disease [1] that has been described in association with mosquito bites and drug hypersensitivity [2-4]. In some patients with eosinophilic cellulitis, peripheral blood mononuclear cells (PBMCs) exhibit a strong response to mosquito salivary gland (MSG) extract. However, it remains unclear whether MSG-stimulated PBMCs promote IL-5 production, which is one of the main pathogenetic factors in patients with eosinophilic cellulitis [5]. Herein, we report a case of eosinophilic cellulitis with a strong response to MSG extract and analyze IL-5 production by PBMCs under MSG stimulation.

A 90-year-old man noticed erythematous papules on his left lower leg after a mosquito bite and subsequently developed edema in the affected area. At first he was diagnosed with cellulitis and administered cefotiam in a nearby dermatology clinic. However, the eruption proved to be intractable. Laboratory examination revealed elevated white blood cells with eosinophilia (5693/μL). After topical application of betamethasone butyrate propionate ointment, the skin eruption gradually improved. Two months later, the patient was bitten again by a mosquito on both legs, resulting in the gradual development of erythema and edema. He was referred to our department for evaluation. Physical examination revealed palpable annular erythema and edema on both legs (Figure A, B). A skin biopsy taken from the site of the erythematous eruption showed an eosinophil-rich infiltration in the dermis (Figure C, D). The blood tests again showed eosinophilia (528/μL). Since a typical flame figure was not observed, we diagnosed the skin eruption as eosinophilic cellulitis, possibly in an early stage. Computed tomography ruled out the presence of internal malignancy. After the administration of oral prednisolone 15 mg per day, his skin eruption improved gradually over the course of 1 month.

Although hypersensitivity to MSG has been reported in patients with eosinophilic cellulitis, it remains unclear whether MSG extract stimulates IL-5 production by PBMCs. To clarify this issue, we performed a lymphocyte stimulation test (LST) with MSG extracts using PBMCs from this patient, as described previously [2,6]. The MSG extracts were prepared from 2 endemic species *Aedes albopictus* and *Culex pipiens pallens*. These extracts induced a high proliferative response in the PBMCs (Figure E). Therefore, we diagnosed the patient's skin eruption as a possible high proliferative response of PBMCs to MSG extracts. Next, to analyze IL-5 production by MSG extract–stimulated PBMCs, the concentration of IL-5 in the supernatants of MSG-stimulated lymphocyte cultures was measured by ELISA and found to be significantly increased under stimulation of MSG by *A albopictus* and *Culex pipiens pallens* (Figure F). Both extracts showed positive reactions in the LST, while PBMCs from a healthy individual showed no

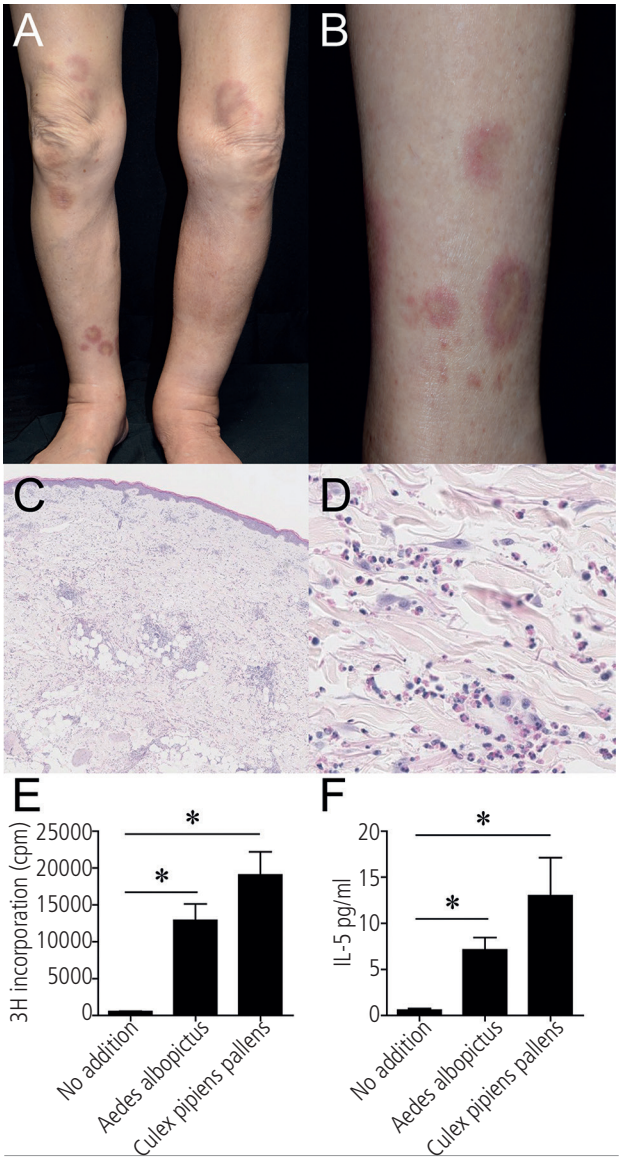

Figure. A, Edema and sporadic annular erythema on the patient's thigh and lower leg (low-magnification view). B, Elevated annular erythema scattered on the patient's lower left leg. C, Inflammatory cells infiltrated in the dermis (low-magnification view). D, Eosinophil-rich infiltration in collagen fiber gap regions in the dermis (high-magnification view). E, PBMC response to MSG extracts. PBMCs were cultured for 72 hours with the indicated MSG extracts. The proliferative responses were assessed by 3H-thymidine incorporation (cpm). F, IL-5 concentration in culture supernatant in (E). $*P > .05$ (t test). MSG indicates mosquito salivary gland; PBMC, peripheral blood mononuclear cells.

significant IL-5 production under the same conditions. These results indicate that MSG might exacerbate IL-5 production by PBMCs and subsequently exacerbate eosinophil activation in patients with eosinophilic cellulitis. Because eosinophilic cellulitis is a relatively rare entity, further investigation is needed to clarify its pathogenesis.

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Conflicts of Interest

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Yu Sawada
Department of Dermatology
University of Occupational and Environmental Health
1-1 Iseigaoka, Yahatanishi-ku
Kitakyushu 807-8555, Japan
E-mail: long-ago@med.uoeh-u.ac.jp