Topical Drug-Induced Acute Generalized Exanthematous Pustulosis Misdiagnosed as an Oral Drug-Related Eruption

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Acute generalized exanthematous pustulosis (AGEP) is characterized by acute onset of fever with a generalized erythematous pustular eruption. It seems that more than 90% of cases with AGEP are drug-induced [1]. The most frequently involved drugs are aminopenicillins, macrolides, antimycotic drugs, calcium channel blockers, carbamazepine, and paracetamol.

We report a severe case of topical drug–induced AGEP that was misdiagnosed as an oral drug–related eruption. A 48-year-old woman who developed a generalized cutaneous eruption without fever was attended several times in the emergency department and was finally admitted.

Physical examination revealed diffuse edematous erythema with nonfollicular pustules all over the body.

The patient had been taking telmisartan and torasemide for several years and reported having taken ibuprofen 7 days before onset. She denied having taken any other drugs during the previous weeks.

The hemogram showed a total white blood cell count of 25 700/mL with 85% neutrophils and 5% eosinophils. The results of serology testing and other laboratory investigations were negative. The skin biopsy was compatible with AGEP.

Antihypertensive drugs and arylpropionic nonsteroidal anti-inflammatory drugs (NSAIDs) were stopped, and the patient was treated with parenteral corticosteroids (6-methyl-prednisolone), antihistamines, and amoxicillin-clavulanic acid. She improved slowly and was discharged from the dermatology department after 14 days taking oral and topical corticosteroids (prednisone and methylprednisolone aceponate).

In our allergy department we performed patch testing with the standard series and 7 NSAIDs including ibuprofen. Reactions were evaluated according to International Contact Dermatitis Research Group guidelines. The results were positive to nickel sulfate (D2–, D3+), caine mix (D2+++, D3+++), ethylenediamine dihydrochloride (D2+++, D3+++), and tixocortol pivalate (D2+++, D3+++) (Figure).

Figure. Positive patch test results to caine mix (+++), ethylenediamine dihydrochloride (+++), and tixocortol pivalate (+++) at 48 hours.

These results led us to question the patient again about any other medication, especially topical medication, and she reported having used a compound for hemorrhoids containing ruscogenin, prednisolone, cinchocaine, menthol, and zinc oxide some days before and during hospitalization.

The patient suffered an acute hypertensive crisis at home approximately 2 weeks after discharge. We reintroduced treatment with telmisartan and torasemide, with no incidents.

The oral challenge test with ibuprofen was negative, and the patient tolerated prednisone and 6-methyl-prednisolone. We suggested patch testing with a corticosteroid series, but she refused more diagnostic tests.

The diagnosis of AGEP was definitive according to EuroSCAR group criteria [1]. We confirmed the diagnosis of drug-induced AGEP by positive patch tests to caine mix, as cinchocaine (a para-amino ester of benzoic acid) was the responsible agent. In some case reports, drug-induced AGEP is diagnosed only by taking a history, with no complementary studies.

Pustular allergic contact dermatitis is a noneczematous form of contact dermatitis. Other forms include erythema multiforme–like eruptions, purpuric contact dermatitis, pigmented contact dermatitis, lichenoid contact dermatitis, acneiform eruptions, dyshidrosiform contact dermatitis, contact granuloma, and hyperkeratotic contact dermatitis [2]. We should consider the possibility of contact dermatitis when faced with one of these entities.

It is very important to take a complete history; however, this should be followed by an allergology workup. It is also important to remember that topical treatments can sometimes cause systemic reactions. Topical bufexamac and other drugs have been reported to induce AGEP [3].

The allergy should be evaluated as soon as possible, because stopping necessary medication can lead to additional medical problems, as with our patient.

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Risk Factors for Systemic Reactions to Allergen-Specific Subcutaneous Immunotherapy

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Allergen-specific subcutaneous immunotherapy (SCIT) is an efficacious treatment modality [1-3], but its safety profile has not been clearly established, especially with reference to risk factors that predict presentation of adverse reactions [4-8]. By identifying risk factors, we can design specific interventions to reduce potentially serious adverse reactions.

We performed a 2-phase study with 568 patients to identify risk factors for SCIT based on safety variables from all doses of immunotherapy given at our unit between 1994 and 2005.

In the first phase, we analyzed risk factors for systemic reactions to SCIT in 277 consecutive patients (group 1, 5768 doses) [9]. Safety procedures in administration of SCIT were modified to reduce systemic reactions. We then administered SCIT to the following consecutive 291 patients (group 2, 4229 doses). Once again, we analyzed risk factors and the modifications to the procedures after the first phase to determine whether the number of adverse reactions had decreased.

We performed a multivariate analysis using the binary logistic regression model as the most appropriate for our objectives.

Significant differences ($P<.05$) were observed between the groups for age (older in group 2), diagnosis (more asthmatics in group 1), and severity of asthma (more patients with moderate asthma in group 1). We found more systemic reactions per dose ($P<.01$) in group 1 (1.6% immediate and 1.2% delayed) than in group 2 (0.5% and 0.6%, respectively). Only noticeable immediate systemic reactions (grades 2 and 3) were analyzed.

The Table shows the results of the logistic regression analysis.

The group factor (group 2) showed reduced risks. The risk factors for an immediate systemic reaction were having received >10 doses in our unit, female sex, a ≥15% fall in peak expiratory flow (PEF), and sensitization to fungi. Diagnosis was not a risk factor. In both groups, the main risk factors were moderate asthma (odds ratio, 4.1; 95% CI, 2.1-8.2) and a fall in PEF at any dose (4.4; 95% CI, 2.3-8.5).

For delayed systemic reactions, belonging to group 2 was a protective factor (Table). Otherwise, receiving >10 doses and occupational exposure were risk factors.

Consistent with other authors, we found sex, severity of asthma, and sensitization to fungi to be risk factors for immediate systemic reaction [9,10]. However, the analysis of risk factors for immediate systemic reaction associated with individual doses showed that some factors can be controlled, for example the presence of a fall in PEF and having an immediate systemic reaction with the previous dose [7].

In group 2, we reduced the next dose by 25% to 50% after an asymptomatic fall in PEF >15%. In group 1 (data not shown), after 116 doses with a fall in PEF, 8 (6.5%) patients had an immediate systemic reaction, whereas in group 2, after 88 falls in PEF, there were no immediate systemic reactions ($P=.039$). Likewise, the presence of an immediate systemic reaction at a dose represents an 8-fold increase in the risk of presenting another reaction at the following dose.

In general, local reactions cannot predict the onset of systemic reactions. However, we found that delayed local reactions led to a 3.6-fold increase in the risk of a delayed systemic reaction at the following dose in all patients, and a 4.3-fold increased risk in asthmatics. In the second group, reducing the dose after a delayed local reaction did not significantly lower the rate of delayed systemic reactions.

Table. Logistic Regression Model for Systemic Reactions Including Group as an Adjustment Variable

		B	Wald	P	Exp(B)	95% CI for EXP (B)	
						Lower	Upper
ISR	Group 2	−.984	8.252	.004	.374	.191	.732
	Doses (>10)	1.103	7.186	.007	3.012	1.345	6.745
	Female sex	.829	6.779	.009	2.292	1.228	4.278
	Unstable asthma	.840	7.844	.005	2.316	1.287	4.169
	Sensitized to fungi	.851	6.119	.013	2.341	1.193	4.595
	Constant	−4.359	41.142	.000	.013		
DSR	Doses (>10)	.862	6.979	.008	2.369	1.249	4.491
	Occupational exposure	1.044	6.380	.012	2.841	1.264	6.388
	Group 2	−1.062	12.149	.000	.346	.190	.628
	Constant	−2.180	48.040	.000	.113		

Abbreviations: CI, confidence interval; DSR, delayed systemic reaction; ISR, immediate systemic reaction.

In the second phase we stabilized asthmatic patients for at least 1 week (instead of the 3 days usually recommended) and thus reduced the incidence of both types of reaction ($P<.0001$).

In conclusion, stabilizing symptomatic asthma for at least 1 week, delaying the dose, and lowering the dose following a fall in PEF >15% seem to be very simple measures for reducing the incidence of systemic reactions to SCIT.

All patients were informed and accepted that all data would be included in the database for scientific purposes. The investigation was conducted according to the principles of the Declaration of Helsinki.

Acknowledgments

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Etiology and Clinical Picture of Anaphylaxis in Ambulatory Patients From Caracas, Venezuela

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Anaphylaxis is a serious and life-threatening reaction whose prevalence is estimated to be between 0.05% and 2% [1]. Its incidence has increased, especially in children [2].

Foods are the most common cause in young people, whereas anaphylaxis induced by drugs and insects and idiopathic anaphylaxis frequently affect older individuals. Less common causes include latex, occupational allergens, inhalants, and nonimmunologic agents.

Despite its frequency and severity, anaphylaxis in Latin America has received little attention. We present our 5-year experience in an outpatient clinic in order to characterize the clinical picture and etiology in this population.

We performed a retrospective review of patients admitted between January 1, 2005 and December 31, 2009. Only patients with a diagnosis of anaphylaxis according to Sampson et al [3] were included. Clinical data included age, sex, symptoms, physical findings, possible etiology, and circumstances surrounding the episode. Diagnostic methods have recently been summarized elsewhere [4] and consisted of historical data, prick tests to confirm immediate-type reactions, and oral challenge tests. The diagnosis was considered to be idiopathic anaphylaxis when the precipitating factor could not be identified [5].

Out of 2421 patients, 179 (7.39%) suffered 1 or more anaphylactic reactions. Females accounted for 126 cases and males 53. Mean age was 32.4 (14.7) years (range, 2-76 y). The group included 12 children—5 girls (41.6%) and 7 boys (58.3%)—with a mean age of 8.7 (3.3) years (range, 2-12 y).

The clinical manifestations are shown in the Table. The most commonly involved sites were the skin, oropharynx, and upper respiratory tract. The gastrointestinal, cardiovascular, and nervous systems were involved less frequently. In children, only cutaneous and respiratory manifestations were observed.

Drugs were the most frequent cause, and were responsible for 98 episodes, followed by foods (43 episodes), oral mite anaphylaxis (13 episodes) [6], other causes (latex [4 episodes], exercise-induced anaphylaxis [3 episodes], intense contact with dogs in an animal facility [1 episode]), and insects (wasp [3 episodes], bees [2 episodes], ants [2 episodes]). No etiology was ascertained in 10 episodes.

The drugs causing anaphylaxis were nonsteroidal anti-inflammatory drugs (NSAIDs) (87 episodes), amoxicillin (2 episodes), ceftriaxone (2 episodes), contrast medium (1

Table. Symptoms and Signs Observed in 179 Patients With Anaphylaxis

	n	%
Cutaneous/Subcutaneous/Mucosal Tissue		
Palpebral angioedema	93	51.9
Diffuse facial angioedema	33	18.4
Lip angioedema	24	13.4
Urticaria	21	11.7
Erythema	14	7.8
Pruritus	10	5.5
Tongue angioedema	10	5.5
Conjunctival edema	4	2.2
Ocular pruritus	3	1.6
Palatal/pharyngeal itching	3	1.6
Tearing	2	1.1
Palatal edema	1	0.5
Hand angioedema	1	0.5
Gingival edema	1	0.5
Respiratory System		
Dyspnea	102	56.9
Laryngeal angioedema	70	39.1
Rhinorrhea	17	9.4
Cough	16	8.9
Nasal congestion	15	8.3
Dysphonia	13	7.2
Wheezing	4	2.2
Sneezing	3	1.6
Stridor	3	1.6
Cyanosis	3	1.6
Respiratory arrest	2	1.1
Acute respiratory failure	1	0.5
Gastrointestinal System		
Dysphagia	9	5.0
Vomiting	2	1.1
Epigastralgia	1	0.5
Diarrhea	1	0.5
Cardiovascular System		
Hypotension	5	2.7
Palpitations	1	0.5
Central Nervous System		
Dizziness	3	1.6
Loss of sphincter control	2	1.1
Unconsciousness	1	0.5
Other		
Diaphoresis	1	0.5
Sensation of obstructed ears	1	0.5

episode), hydrocortisone (1 episode), rocuronium (1 episode), fentanyl (1 episode), lansoprazole (1 episode), doxorubicin (1 episode), and dinitrochlorobenzene (1 episode). Patients with NSAID-induced anaphylaxis were cross-reactors (76) and single reactors (11). The foods involved were shellfish (30 patients), nuts (3 patients), lentils (2 patients), peanut (2 patients), tuna (1 patient), cheese (1 patient), beef (1 patient), apple (1 patient), corn (1 patient), and yucca (1 patient).

Although severe, frequent, and increasingly common

worldwide [2], anaphylaxis has received little attention in Latin America. Many cases are neither diagnosed nor reported, patients are not referred, and mortality rates are unknown.

We observed that anaphylaxis occurred mainly in women and that drugs were the most common cause, followed by foods. NSAIDs were involved in almost half of all cases, probably because they are sold over the counter. Antibiotics must be prescribed by a physician. Nevertheless, in other series [7], antibiotics were the predominant agent, followed by anti-inflammatory drugs.

In the case of foods, shellfish were often involved, and anaphylaxis may have resulted from cross-reactivity between shellfish and mite tropomyosin, since many patients are also sensitized to mites [8]. Fruits frequently inducing anaphylaxis in other countries, such as nuts, peaches, apples, and kiwi, are relatively expensive, and not commonly consumed.

Mites are recognized as a source of hidden food allergens. In the present study, we observed that 13 patients developed oral mite anaphylaxis [6], which is common in tropical climates, although cases have been reported in temperate regions [9]. Other causes (latex, exercise, inhalant allergens, and insects) were less frequent.

In conclusion, we describe the most common manifestations and causes of anaphylaxis in patients from Caracas. Due to the scarcity of studies in Latin America, patients may not be aware of this condition and, consequently, do not obtain optimal diagnosis and therapy.

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Aquagenic Urticaria in 2 Adolescents

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Aquagenic urticaria (AU) is a type of urticaria that occurs after direct contact with water, regardless of its temperature. It was first described in 1964 [1]. We present the cases of 2 adolescent boys with AU.

A 17-year-old boy and a 15-year old boy presented with a 10-month and 3-month history, respectively, of erythema, small wheals, and pruritus after contact with water. Symptoms developed after taking a shower or swimming (sea and swimming pool), regardless of the temperature and type of water. Lesions appeared predominantly on the trunk and usually disappeared spontaneously in minutes. Hives were not triggered by other conditions such as exercise, sweating, stress, or cold weather. No similar incidents were reported in other family members.

Physical examination was unremarkable and laboratory results were all within normal limits. The ice cube test and exercise test did not reveal urticaria. Finally, water challenge tests were performed by applying a towel soaked in tap water at body temperature on the upper trunk for 20 minutes. Within 5-10 minutes, the patients reported pruritus, and multiple hives were noted on the contact area (Figure). The lesions resolved spontaneously in 30 minutes. AU was diagnosed and an

Figure. Small erythematous papules on the upper trunk of the second patient.

antihistamine (desloratadine) was prescribed before exposure to water. Our patients remained asymptomatic after 9 months and 3 months of follow-up, respectively.

AU is an uncommon type of physical urticaria. It is seen mainly in women, and symptoms often start at the onset of puberty [2]. Most cases are sporadic, although familial incidents have also been reported [3,4].

Our patients were adolescent boys from different families and their symptoms started at puberty, which is consistent with previous data reported by Dice [2]. The second patient was atopic to grass pollens and had family members with atopic diseases. However, no evident association between atopy and AU has been found to date. Systemic findings associated with urticaria have been reported, although our patients did not have any accompanying symptoms [5,6].

Various types of physical urticaria, such as dermographism, cholinergic urticaria, or cold urticaria may be associated with AU [5-8]. Cold urticaria and cholinergic urticaria are major differential diagnoses for AU. Wheals are similar in both AU and cholinergic urticaria; therefore, triggering factors must be investigated in order to exclude cholinergic urticaria. Our patients' symptoms were not associated with any triggers, and the results of the ice cube test were negative.

A water challenge test performed by applying wet cloths at body temperature for 20 minutes is recommended for the diagnosis of AU [8]. After the challenge test, both patients showed urticarial swellings on the contact areas, thus leading to the diagnosis of AU.

The pathogenesis of AU remains unknown, although several mechanisms have been proposed. Shelley and Rawnsley [1] initially concluded that water reacting with sebum generates a substance causing release of histamine from perifollicular

mast cells. Sibbald et al [9] postulated a relationship between penetration of water into skin components and swelling. Czarnetzki et al [7] concluded that a water-soluble antigen in the epidermal layer that penetrates into deeper levels of skin initiates a reaction causing release of histamine from sensitized mast cells in the dermis. Acetylcholine and methacholine are thought to be the responsible mediators in pathogenesis; however, results for the mechanisms induced by these mediators are conflicting [6,7,9,10].

In conclusion, although the clinical picture of AU and diagnostic procedures are well established, pathogenesis remains unclear. We report the first observation of this rare condition in Turkish adolescents.

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A Comparison Between Morphine and Histamine as a Positive Control Agent for Intradermal Skin Testing: An Evidence-Based Study

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Intradermal tests (IDTs) play an important role in the diagnosis of immediate hypersensitivity reactions, particularly those to drugs and venoms [1,2]. A positive control is required to ensure the reliability of such tests. Currently, 0.1 mg/mL histamine base is recommended as a positive control for IDTs [3]. The availability of histamine solution, however, is often restricted to special clinics since its role other than that of a positive control agent is rather limited.

Certain drugs in the opiate group, such as codeine, are able to induce skin wheal reactivity [4]. Nevertheless, codeine is mostly available as an ingredient in cough suppressants and pain relievers, but not as a drug in itself, making it impractical for IDT use. The availability of morphine in general hospitals makes it more practical for use as a positive IDT control by general physicians or in nonspecialist settings. The purpose of this study was to find morphine concentrations that yield comparable skin reactivity to standard histamine as a positive control for IDTs.

Twenty-five healthy volunteers (16 males and 9 females with a mean age of 28.2 years [range, 23-49 years]) with no history of opiate hypersensitivity were enrolled in the study. Eighteen of the participants were nonatopic and 7 had allergic rhinitis with positive skin tests to aeroallergens. Volunteers who had received antihistamines or montelukast in the 7 days before the test, cromolyn in the 14 days before

the test, or systemic corticosteroids in the month before the test were excluded. Histamine phosphate at a concentration of 0.05 mL (0.275 mg/mL of Histatrol, Alk-Abelló, Round Rock, Texas, USA), equivalent to 0.1 mg/mL histamine base, and 3 concentrations of morphine sulfate (0.01, 0.1, and 1.0 mg/mL) were intradermally injected on the forearm volar surface with a distance of at least 2 cm between injection sites. Skin wheal diameters were serially measured at 5-minute intervals from 15 to 30 minutes after injection. The study was approved by the local ethical committee and all the volunteers gave their informed consent. Because the skin wheal diameters from each test solution had a normal distribution, the *t* test was used to compare wheal diameter means between each morphine concentration and histamine and between patients of different sex and atopic status. Statistical analysis was performed using SPSS 15.0 for Windows and *P* values of <.05 were considered significant.

The results showed that the size of skin wheals induced by morphine sulfate was dose-dependent and correlated with skin wheal response to histamine. As wheal size read at 15 minutes after histamine injection is a standard IDT positive control, morphine-generated wheals were compared to this reference point (Table). Morphine at 0.1 mg/mL yielded comparable wheal sizes to histamine control at all time points, and sizes read 15 or 20 minutes after injection were equivalent to those produced by histamine at 15 minutes. Morphine at 1 mg/mL yielded larger wheal sizes at each time point than those produced by histamine at 15 minutes. Finally, at 15 minutes, 0.01 mg/mL morphine yielded smaller wheal sizes than standard histamine. Wheal diameters increased in size from 20 minutes onwards but it would be difficult to compare these with wheals produced by test allergens that are normally read within 20 minutes of injection [5]. Wheal diameters in male and atopic volunteers were slightly larger than those in female and nonatopic volunteers, respectively, as previously reported [6], although statistical significance was not reached. There were no serious consequences of morphine administration.

This study confirms that morphine is a reliable IDT positive control agent. Morphine sulfate 0.1 mg/mL yielded comparable skin wheal response to that obtained with standard histamine when interpreted 15 to 20 minutes after the test. We suggest that morphine is a good candidate for use as a positive control agent for IDTs in nonspecialist settings where histamine solution may not be available.

Table. Skin Wheal Reactivity (Diameter in mm) From Different Morphine Concentrations Compared to Standard Histamine at Various Time Points

Reading Time After Intradermal Test	15 Min	20 Min	25 Min	30 Min
Histamine 0.1 mg/mL	12.3±0.5	14.1±0.5	15.1±0.8	15.4±0.8
Morphine 0.01 mg/mL	9.9±0.4	11.3 ±0.4[a]	12.4±0.6[a]	12.8±0.6[a]
Morphine 0.1 mg/mL	11.9±0.5[a]	13.2±0.6[a]	14.0±0.6	14.4±0.6
Morphine 1.0 mg/mL	13.2±0.4	14.7±0.5	15.7±0.6	16.3±0.5

[a]Concentrations of morphine and reading points that yielded comparable wheal sizes with that of standard histamine read at 15 minutes after injection.

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Rapid Immunochromatography of Total Tear Immunoglobulin E in Allergic Conjunctivitis With Allerwatch

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Measurement of total tear immunoglobulin (Ig) E is useful for the diagnosis of allergic conjunctivitis [1,2]. Several research groups have reported methods for measuring total tear IgE by immunochromatography [3-5], and more recently, a new commercial kit called Allerwatch, which is a rapid immunoassay for measuring total tear IgE levels, was developed and released by Hitachi Chemical Co., Ltd. and Wakamoto Pharmaceutical Co., Ltd. in Tokyo, Japan. The aim of this study was to ascertain whether or not Allerwatch could be employed as a screening test for the diagnosis of allergic conjunctivitis.

The study was performed in accordance with the Helsinki Declaration of 1975 and its 1983 revision. Institutional Review Board approval was provided and informed consent was obtained from all participants. Fifty-nine outpatients with acute seasonal allergic conjunctivitis treated at our hospital between February and May 2009 (allergic group) and 42 age- and sex-matched healthy controls with no history of allergic disease (control group) were enrolled (Table). Allergic conjunctivitis was diagnosed according to published guidelines for the diagnosis and treatment of conjunctivitis [6]. Tests involved slit lamp examination to detect findings such as conjunctival follicles, papillae, and redness and an analysis of the history of seasonal symptoms such as ocular itching and tearing without proliferative lesions. Furthermore, all the patients showed total serum IgE levels above 100 kU/L (range, 120-970 kU/L) in a paper radioimmunosorbent assay (Phadezym PRIST; Pharmacia, Uppsala, Sweden) and cedar pollen or cypress pollen specific IgE levels above 0.70 kU/l with the CAP-RAST system (Pharmacia). Patients were enrolled if they had moderate or severe allergic conjunctivitis according to the classification proposed by The Japanese Ophthalmological Society [7]. Determination of total IgE was performed with the Allerwatch test according to the manufacturer's instructions. When values are normal (<2.0 KU/L), no lines form on the display screen of the kit. The results were divided into 3 grades.

Results were positive in 57/59 patients with allergic conjunctivitis (96.6%) and negative in all of the controls (0.0%,

Table. Comparisons Between Control Group and Allergic Group

		Control Group		Allergic Group	P Value
Patients, No.		42		59	
Age, mean (SD), y		24.8 (8.0)		24.1 (13.5)	NS[a]
Male:female, No.		20:22		27:32	NS[b]
Allerwatch Test	Grade	Control Group		Allergic Group	P value
Positive	2	0		34	
Positive	1	0		23	<.001[c]
Negative	0	42		2	
Sensitivity, %			96.6		
Specificity, %			100.0		
Positive predictive value, %			95.5		
Negative predictive value, %			100.0		

Abbreviation: NS, not significant.
[a]Unpaired t test.
[b]χ^2 test.
[c]Mann-Whitney U test.

Table). There was a significant difference between patients and controls in terms of positive results (P<.001, Fisher exact test) and the grade obtained (P<.001, Mann-Whitney U test). Sensitivity, specificity, and positive and negative predictive values are shown in the Table.

The Allerwatch test showed very high sensitivity (96.6%) and specificity (100.0%) in our series. These rates are similar to or higher than previously reported rates [3,4]. Sirbikate et al [3], for example, reported sensitivity and specificity rates of 93.8% and 89.7%, respectively, for the Lacrytest allergic conjunctivitis diagnosis kit (Adiatec S.A, Nantes, France). Because total IgE in tear fluid increases with the severity of allergic conjunctivitis [2,5], determination of total tear IgE levels is useful not only for making a clinical diagnosis of allergic conjunctivitis but also for the assessment of severity [5]. Because we studied patients who had moderate to severe allergic conjunctivitis, we need to evaluate the sensitivity of this kit in patients with mild allergic conjunctivitis.

Measurement of IgE is quicker with the Allerwatch kit than with a standard enzyme-linked immunosorbent assay. IgE levels can be clearly identified by viewing the test line and we were able to assay total tear IgE in 15 minutes (including the time for tear fluid collection). This could be of considerable benefit to patients because it would mean that allergic conjunctivitis could be diagnosed at the first visit to a clinic. The test strip is ready for immediate use and the sterile strip is simply placed at the lower fornix of the conjunctiva. The Allerwatch test thus is a rapid, sterile, and noninvasive method for assessing allergic conjunctivitis.

In conclusion, this study demonstrated that Allerwatch is a rapid, simple screening test for allergic conjunctivitis that can also be used for assessing the severity of this condition. In the future, we will investigate the relation between the severity of allergic conjunctivitis and total IgE levels in tear fluid.

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Fixed Drug Eruption Due to Propofol After an Intradermal Test

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Propofol is a short-acting anesthetic that is administered for induction and maintenance of general anesthesia. Its secondary effects are well known, in particular bronchospasm [1] and generalized metabolic disorders, sometimes accompanied by rash; these effects generally occur after prolonged infusion of the drug at high doses [2,3]. However, allergic reactions are uncommon and account for less than 2% of all reactions to general anesthetics, although there have been reports of immunoglobulin (Ig) E–mediated reactions (generally urticaria but sometimes even anaphylactic reactions) [4]. Anaphylactoid reactions are more common. Although propofol is not contraindicated in patients who are allergic to egg or soya, some reactions have been associated with the presence of soybean oil or egg lecithin in the solvent of certain commercial propofol preparations [5].

A 72-year-old woman diagnosed with arterial hypertension and type II diabetes mellitus attended our unit. Several years previously, she had developed a skin lesion on the margo medialis tibiae of her right leg in association with the administration of general anaesthesia during surgery to correct a foot defect. She had not needed general anesthesia since then, but was scheduled to undergo surgery for a cervical tumor, so an allergy workup was decided upon.

The allergy workup included skin prick tests and intradermal tests that were performed according to the usual protocol at our unit. The drugs tested were muscle relaxants (vecuronium, cisatracurium, rocuronium, and succinylcholine), hypnotic agents (etomidate, ketamine, and propofol), fentanyl, benzodiazepines, and bupivacaine. The patient also underwent skin prick testing with a commercial latex extract (ALK-Abelló, Madrid, Spain), egg, and soybean (LETI, Madrid, Spain). Saline phenolated solution and histamine 0.1 mg/mL were used as negative and positive controls, respectively. All the results were negative at 30 minutes and 2 hours. Seventy-two hours after the tests, the patient returned to our unit with 2 slightly pruriginous macules on the margo medialis tibiae of the right leg. We also observed an erythematous papule at the site of the intradermal test for propofol (0.1 mg/mL). Biopsies of the lesions were taken and revealed hydropic degeneration of the basal layer of the epidermis, pigmentary incontinence, and incipient exocytosis from a chronic perivascular infiltrate of the papillary dermis. Necrotic keratinocytes (Civatte bodies) with eosinophilic cytoplasm and pyknotic nuclei were also
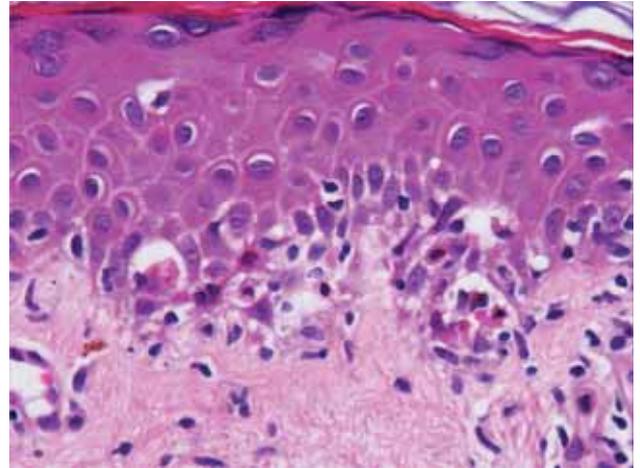

Figure. Biopsy of the papule obtained in the intradermal test (original magnification ×40)

observed in the basal epidermis (Figure). These findings were all suggestive of fixed drug eruption in this clinical setting. Three months later, patch tests with propofol (5% in water) were performed on the back and in the previously affected area of the leg, with positive results (++) at both sites.

In summary, we present a case of fixed drug eruption induced by intradermal testing with propofol. To our knowledge, this is the first report of such a case in the literature. It is possible that the number of delayed reactions to anesthetics are underestimated.

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Nonimmediate Systemic Hypersensitivity Reaction to ß-Lactam Intradermal Tests

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Figure. Positive responses to ampicillin and amoxicillin intradermal tests.

ß-Lactams are one of the main causes of allergic reactions to drugs and are reported to induce both immediate and nonimmediate reactions. Immediate reactions, usually induced by an immunoglobulin (Ig) E–mediated mechanism, occur within an hour of the last drug administration. Nonimmediate reactions generally occur 1 to 48 hours after the last dose, but they can also appear later; they are often induced by a delayed T cell–dependent type of allergic reaction [1]. Maculopapular exanthema is the most common nonimmediate reaction.

The diagnosis of ß-lactam allergic reactions is now well established, with skin testing and drug provocation tests considered to be the main diagnostic tools [2,3]. We describe a rare systemic nonimmediate reaction to ß-lactam intradermal tests.

A 55-year-old woman was referred to our clinic because of a maculopapular eruption that had appeared almost 15 years earlier, during treatment with amoxicillin for acute tonsillitis. The exanthema had appeared on the third day of treatment, almost 2 hours after the last dose, and mainly affected the face, the neck, and the upper chest. Within 24 to 36 hours, it had spread to the whole body and was accompanied by redness of the palms and soles and excessive pruritus. The symptoms lasted for almost 2 weeks and the patient was treated with oral H_1-antihistamines and a short course of oral methylprednisolone. The personal and family history for atopic diseases was negative and the patient reported no history of other drug allergies.

The allergy workup revealed normal serologic specific IgE values for penicilloyl G and V as well as for ampicilloyl and amoxicilloyl (<0.35 Ku/L; Phadia ImmunoCap, Uppsala, Sweden). Skin tests and intradermal tests were carried out according to the following sequence: (i) prick tests with penicilloyl-polylysine (PPL; benzylpenicilloyl poly-L-lysine 0.04 mg and Mannitol 20 mg per 1.0 mL of diluent); minor determinant mixture (MDM; sodium benzylpenicillin 0.5 mg, benzylpenicilloyl acid 0.5 mg, sodium benzylpenicilloate 0.5 mg and mannitol 20 mg per 1.0 mL of diluent) (Diater TM, Madrid, Spain); penicillin G (10 000 IU/mL); penicillin V (40 000 IU/mL); amoxicillin (20 mg/mL); ampicillin (20 mg/mL); cefuroxime (20 mg/mL); cefaclor (20 mg/mL); and (ii) intradermal tests (1/100, 1/10 and full-strength concentrations) at 20-minute intervals. Exceptionally, due to the nonimmediate nature of the reaction, full-strength intradermal tests were not performed with ampicillin or amoxicillin. Responses were evaluated at 20 minutes and at 6, 24, and 48 hours.

At the 24-hour reading, the patient exhibited positive responses in intradermal tests with both concentrations of ampicillin and amoxicillin (indurated wheals larger than 10×10 mm with erythema) as shown in the Figure. Besides, the patient reported that almost 12 hours after the skin tests, she had developed fever (38.5ºC) accompanied by the gradual appearance of maculopapular lesions and erythema of the palms and soles. Physical examination 24 hours after skin testing was normal except for a maculopapular eruption that was more intense on the upper trunk and chest and almost identical to the eruption that had brought the patient to be referred to our clinic. She was treated with a low dose of oral prednisolone. Her temperature was normal from the first day of treatment, and the exanthema and positive intradermal test responses lasted for 72 to 96 hours. The prick and intradermal tests with the rest of the reagents were all negative.

Systemic reactions to ß-lactam skin tests are rarely reported and in the vast majority of cases are immediate [4,5]. Our case is an example of an extremely rare nonimmediate reaction and the offending antigenic determinant is probably the aminobenzyl side chain shared by ampicillin and amoxicillin [6]. Notably, memory cells that are responsible for nonimmediate reactions are still present and trigger an immunologic response even with the low antigenic concentration that is used in skin testing. Unfortunately, our patient was reluctant to undergo a provocation test to penicillin V.

In conclusion, this case illustrates that intradermal tests should be performed cautiously and the importance of their late reading must not be underestimated. It also illustrates that nonimmediate systemic reactions, even rarely, can occur after intradermal testing.

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Antituberculosis Drug-Induced Drug Rash With Eosinophilia and Systemic Symptoms Syndrome Confirmed by Patch Testing

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Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a rare and potentially fatal drug reaction characterized by fever, skin rash and internal organ abnormalities [1]. There have only been 2 case reports describing DRESS syndrome caused by antituberculosis drugs [2,3]. We report a case caused by first-line antituberculosis drugs used to treat ureteral tuberculosis and confirmed by patch testing.

A 72-year-old woman was referred to our allergy department because of a generalized maculopapular rash that had appeared 4 weeks after she had started taking antituberculosis drugs (isonizid, rifampin, ethambutol, and pyrazinamide) for ureteral tuberculosis. On physical examination, a generalized, diffuse, maculopapular erythematous rash was noted over the trunk and limbs and there was also severe facial angioedema. The laboratory studies showed eosinophilia (total white blood cells, 15 090/mm³; eosinophils, 64.3%), while the liver function tests revealed aspartate aminotransferase 45 IU/L (normal, 10-35 IU/L), and alanine aminotransferase 52 IU/L (normal, 0-35 IU/L) (Table). Serologic tests for several autoantibodies, viral markers, and infectious organisms including parasites were all negative. The antituberculosis drugs were discontinued and the patient was treated conservatively with antihistamines and topical corticosteroids. (Systemic corticosteroids were avoided due to the risk of tuberculosis dissemination.) Ten days after discontinuation of the antituberculosis drugs and with no additional specific treatment, the skin lesions had improved dramatically. Six weeks after discharge from the hospital, the patient had no cutaneous or biochemical abnormalities and we performed a patch test with 4 antituberculosis drugs on her upper back. Each tablet was crushed and added to white petrolatum at 50%. At 48 hours, a diffuse erythematous rash was seen around the isoniazid, rifampicin, and ethambutol patches. We then performed serial oral provocation tests with pyrazinamide as follows: day 1, 1/4 tablet (125 mg); day 2 (250 mg); and day 3 (500 mg). On day 3, the patient developed a skin rash on the upper limbs but showed no systemic symptoms or biochemical abnormalities. We successfully administered kanamycin, levofloxacin, and prothionamide to treat the patient's ureteral tuberculosis following serial provocation testing, with no apparent side effects.

DRESS syndrome is an idiosyncratic severe adverse drug reaction that begins in the first 2 months (average 3 weeks) after initiation of the offending drug [4]. In our case, it developed 4 weeks after the introduction of antituberculosis drugs. The patient had no known exposure to other medications that have been implicated in the development of DRESS syndrome. Several objective methods to detect the association between a suspicious drug and DRESS syndrome have been recommended. Helpful diagnostic tools include the in vitro lymphocyte toxicity assay, the lymphocyte transformation test, and in vivo patch testing [5,6]. As patch testing is less cumbersome and more reliable, it is more frequently used in cases of diagnostic uncertainty [7]. However, the diagnostic accuracy of the patch test in DRESS syndrome is currently unknown. In our case, patch test results showed a negative response to pyrazinamide, but serial oral provocation with the same drug led to the reappearance of the skin lesions. The pathogenetic mechanisms through which antituberculosis drugs cause DRESS syndrome are not known. In this study, the patient showed sensitization to 3 antituberculosis drugs in patch tests. Positive patch test results might represent nonspecific irritant reactions but we did not use serial increasing concentrations or test healthy controls. However, we suspect that individual differences, especially genetic factors, may have an important role in sensitization to multiple drugs. Further studies are required to evaluate the pathogenetic mechanisms associated with multiple antituberculosis drug-induced DRESS syndrome.

Table. Laboratory Values and Clinical Characteristics of Patient

	Days After Admission						
	0	5	7	8	9	10	16
Highest temperature, °C	36.6	37.2	36.8	36.7	36.2	36.5	36.7
White blood cells, No./μL	15 090	12 300	8380	8680	8310	7860	6850
Eosinophil, %	64.3	45.1	30.9	35.6	29.6	21.1	17.2
Aspartate aminotransferase, IU/L	45	116	96	97	100	94	32
Alanine aminotransferase, IU/L	52	89	101	114	125	129	46

In conclusion, this case suggests that antituberculosis drugs might be new candidates for DRESS syndrome.

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