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SYSTEMIC CONTACT ALLERGY TO PENICILLIN AFTER PRICK AND INTRADERMAL TESTS

Systemic contact dermatitis (SCD) is a type of contact hypersensitivity reaction induced by ingestion or other systemic exposure to a contact allergen in an already sensitized person. Usually the initial sensitizing exposure has happened by topical application, but reexposure by the oral, intravenous, or inhalation routes can cause SCD. It appears that both humoral and cellular immune responses are involved in this situation.¹ Baboon syndrome may be seen as a particular form of SCD, with a distribution pattern confined to the intertriginous areas and with nickel, mercury, and drugs acting as inducers.² The designation *baboon syndrome*, which emerged from the characteristic, bright red, well-demarcated eruption predominantly located on the buttocks and genital area (reminiscent of the red bottom of the baboon), has recently been replaced by the term *symmetrical drug-related intertriginous and flexural exanthema* (SDRIFE), which refers to the distinctive clinical pattern of this drug eruption. Several diagnostic criteria have been proposed: (1) exposure to a systemically administered drug either at the first or repeated dose (excluding contact allergens); (2) sharply demarcated erythema of the gluteal or perianal area and/or V-shaped erythema of the inguinal or perigenital area; (3) involvement of at least 1 other intertriginous or flexural localization; (4) symmetry of affected areas; and (5) absence of systemic symptoms and signs.³

Late positivity of a prick test result to amoxicillin supports the role of this agent as the culprit drug in some cases of SDRIFE and suggests the involvement of type IV hypersensitivity reaction.⁴

We report a case of a 32-year-old man with no previous history of atopy who appeared with pruriginous erythema involving the bilateral aspects of the axillae, groin, and popliteal fossa that had a spontaneous clinical resolution in the following 2 weeks. Within the previous 24 hours, he had been administered intramuscular penicillin G benzathine, 2,400,000 U, and oral ibuprofen, 600 mg. Ten months previously, he had taken ciprofloxacin for acute prostatitis.

The allergy workup was performed and results were as follows. The serum level of total IgE was normal and specific IgE test results for penicillin were negative. The results of prick and intradermal tests performed with an aqueous solution of a commercial benzylpenicilloyl-polylysine (5×10^{-5} mM/L; Diater, Madrid, Spain), a minor determinant mixture (2×10^{-5} mM/L; Diater), penicillin G (10,000 IU/mL; Atral Cipan, Lisbon, Portugal), amoxicillin-clavulanic (20 mg/mL; Labesfal, Lisbon, Portugal), and ampicillin (20 mg/mL; Atral Cipan) were negative at 20 minutes.

Eight hours after the skin tests had been performed, the patient was admitted to the inpatient unit of the dermatology department. In the first 2 hours, a pruriginous erythema appeared on the penicillin, amoxicillin, and ampicillin inoculation sites and disseminated to the posterior cervical area, groin, axillae, forearms, popliteal fossa, and penis glans (Figure 1). A cutaneous



Figure 1. A pruriginous erythema on the penicillin, amoxicillin, and ampicillin inoculation sites that disseminated to the posterior cervical area, groin, axillae, forearms, popliteal fossa, and penis glans.

biopsy specimen of the lesions showed a superficial perivascular infiltration with lymphocytes, histiocytes, eosinophils, and epidermal spongiosis.

Patch tests with a standard series adopted by the Portuguese Study Group of Contact Dermatitis and allergens from Chemotechnique, complemented with penicillins and ibuprofen, were performed. Readings following the patch test reactions according to the International Contact Dermatitis Research Group were performed at 48 and 96 hours: standard series results were negative, 10% potassium penicillin G, 10% amoxicillin, and 10% ampicillin test results were positive at both readings, and 10% cephadrine and 10% ibuprofen test results were negative.⁵

To evaluate cross-reactivity between penicillins and cephalosporins, the patient underwent prick and intradermal tests to cefuroxime (2 mg/mL; Labesfal) and ceftriaxone (2 mg/mL; Labesfal). No immediate or delayed reactions were observed.

In accordance with current guidelines, we performed oral and intravenous drug provocation tests, respectively, with cefuroxime and ceftriaxone. Increasing doses were administered with an interval of 30 minutes between doses, a total cumulative dose of 500 mg being reached for each drug (oral cefuroxime protocol: 50 mg, 150 mg, 250 mg; intravenous ceftriaxone protocol: 10 mg, 40 mg, 100 mg, 150 mg, 200 mg). Both drug provocation test results were negative.

Penicillins are low-cost and highly efficient antibiotics but are the most frequent cause of allergic drug reactions, both immediate and nonimmediate.⁶ Such reactions must be diagnosed and cross-reactivity

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tion with cephalosporins assessed so that appropriate future antimicrobial therapies can be chosen.

Patch tests are considered to be the most reliable diagnostic procedure for allergen identification in patients with SDRIFE because of the probable role of a type IV hypersensitivity mechanism. Surprisingly, skin tests have been performed in only a few patients, and positive skin test results in a SDRIFE-like systemic reaction have not yet been published, making our patient the first published case, to our knowledge, of SDRIFE with positive patch and intradermal test results to penicillin.⁴

Third-generation cephalosporins have proven to be a safe alternative in this patient, which is usually the case in patients with β -lactam antibiotic allergy; cross-reactivity between penicillin-aminopenicillin and third-generation cephalosporins is infrequent.⁷

In conclusion, we emphasize the importance of an allergy workup, including skin patch tests, in the study of patients presenting with an exanthema and suspected β -lactam allergy, namely, in cases of SDRIFE.

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AUTOLOGOUS PLASMA SKIN TEST

Chronic urticaria (CU), defined as the recurrence of wheals with or without angioedema occurring daily or almost daily for more than 6 weeks, is a common disease that may severely worsen the quality of life.¹ CU is often an autoimmune disorder sustained by circulating histamine-releasing autoantibodies directed against the α -subunit of the high-affinity IgE receptor (Fc ϵ RI α) or against IgE.² The autologous serum skin test (ASST) is the most frequently used in vivo screening test for the diagnosis of autoimmune urticaria, with a sensitivity of approximately 65% to 70%.³ Recent studies have shown that autoreactivity can be increased up to 90% if the autologous plasma skin test (APST) is used.⁴ An increase in prothrombin fragment F1+2, activated factor VIIa, and D-dimer levels has also

been observed in patients with CU, showing that the coagulation cascade, starting from the tissue factor pathway (extrinsic pathway) and leading to the thrombin generation, is activated in these patients.⁵ Skin eosinophils represent the main source of tissue factor and vascular endothelial growth factor, both of which are increased in patients with CU.⁶

The aim of the current study was to investigate skin autoreactivity by using autologous plasma anticoagulated with sodium citrate and compare it with ASST results in patients with CU. Adult patients with CU followed up at our allergy department who were between 18 and 80 years old and had active urticaria in the 6 months before the study were invited to participate. CU was diagnosed on the basis of the appearance of continuous or recurrent hives, with or without angioedema, for more than 6 weeks.¹ Patients with physical urticaria, including dermatographism, were excluded. Blood tests; thyroid hormone (thyrotropin and T4) measurement; tryptase measurement; serologic screening for hepatitis A, B, and C; measurement of immunoglobulins (IgG, IgA, IgM, and IgE); measurement of complement (C3 and C4); screening for parasites in stools; and measurement of autoantibodies and specific IgE for *Anisakis* were performed in all patients. We also investigated the presence of angioedema associated with any episode of urticaria. Antihistamines were withdrawn at least 7 days before skin test performance. All selected patients and 10 healthy controls underwent intradermal tests with 0.05 mL of autologous serum and plasma. Saline and histamine were used as negative and positive controls, respectively. A wheal-and-flare reaction with a wheal diameter of at least 3 mm in the absence of any reaction to saline at 30 minutes was considered a positive result. Statistical analysis was performed using the χ^2 and Mann-Whitney tests. $P < .05$ was considered significant.

Thirty-one patients were included, 5 male and 24 female, with ages ranging from 18 to 80 years. None of the patients reacted to the intradermal injection of saline, and the results of skin prick tests with 10 mg/mL of histamine were positive in all cases. None of 10 healthy controls showed any reactivity to the autologous serum and plasma injections. Twelve out of 31 patients (39%) scored positive on the APST, and 2 out of 31 (6%) scored positive on the ASST ($P = .002$). The 2 patients with positive ASST results also had positive APST results. These percentages are lower than previously reported,⁴ and the reason may be that only 11 of the 31 patients had active urticaria, with the presence of wheals, when the tests were performed. Indeed, a positive APST result was found in 73% of the patients with active urticaria (8/11) and in only 20% of the patients (4/20) with inactive urticaria ($P = .007$). The difference between positivity for APST and ASST is higher than reported by others groups.⁷ Different methods and interpretation and degree of activity of urticaria may be the cause of this difference. Concomitant episodes of angioedema with any urticaria episodes were found in 9 out of 31 patients with CU, none of them with an active angioedema at the moment the test was performed. Eight of these 9 patients (89%) had a positive APST result. In contrast, only 4 out of the 22 CU patients without associated angioedema (18%) had positive APST results ($P < .001$). We have not found any other significant differences in the remaining parameters analyzed.

In summary, in this study performed in a Spanish population to assess reactivity to autologous serum and plasma in patients with CU, we found that the APST has a higher sensitivity than the ASST and seems sufficient to assess skin autoreactivity because positive responses on the ASST were only observed in those patients with positive APST results. Reactivity to the APST was significantly associated with the activity of urticaria, and it is significantly higher in patients with angioedema associated with urticaria.

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