

**Possible anergy after
generalized orally elicited
allergic contact dermatitis
to corticosteroid**

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skin hyporeactivity.

Anergy is defined as a diminished reactivity to one or more specific antigens (1). Failure to respond to specific antigens might be the result of a faulty immune response or a defective inflammatory response, or both (2). Skin anergy could be responsible for false-negative patch test results. We report a patient with a history of multiple topical corticosteroid allergic contact dermatitis (ACD), who subsequently developed a putative generalized orally elicited ACD to corticosteroid. Surprisingly, he had a negative patch test 2 weeks after discontinuing corticosteroid,

possibly because of anergy. We performed another patch test 6 weeks after the eruption. This time, he developed positive reactions to multiple corticosteroids.

Case Report

A 66-year-old physician was referred for an assessment of generalized eruption 3 days after taking methylprednisolone (Medrol[®] Dosepak[™]; Pfizer's U.S. Pharmaceuticals Group, New York, NY) for tendinitis. Physical examination showed a generalized erythematous maculopapular rash especially at the thigh. His medical history was also significant for asthma, elevated cholesterol, and arthritis. Medication history included cromolyn sodium (Nasalacrom), allopurinol, triamcinolone acetonide (Nasacort[®] aq.), atorvastatin (Lipitor[®]), tamsulosin hydrochloride (Flomax[®]), carbido-
pa/levodopa, valsartan (Diovan[®]), furosemide (Lasix), azelastine hydrochloride (Astelin[®] nasal spray), pramipexole dihydrochloride (Mirapex[®]), diclofenac sodium (Voltaren[®]), and ibuprofen. He had multiple drug allergies to labetalol hydrochloride, acetaminophen (Tylenol[®]), penicillin, cefaclor (Ceclor[®]), tetracycline, indomethacin (Indocin[®]), naproxen (Naprosyn[®]), and trimethoprim/sulfamethoxazole (Bactrim). There was no personal or family history of atopy.

In 2000, a long-standing dermatitis led to diagnostic patch testing showing positive reactions to multiple corticosteroids – budesonide, betamethasone valerate, triamcinolone, dexamethasone, clobetasol, and alclometasone – some of which were thought to be false-positive reactions because of the presence of excited skin syndrome (3). Provocative use tests (PUT)/repeated open application test (ROAT) (twice daily for 14 days to the cubital fossa) were performed and confirmed the relevance of the patch test reactions. He denied any history of intolerance to systemic corticosteroids.

To clarify the nature of his recent generalized eczema, patch test with the corticosteroid series CS-1000 (Chemotechnique, Malmo, Sweden) was performed 2 weeks after discontinuing corticosteroid. Methylprednisolone was not tested, as this was not available.

To our surprise, the results were all negative on 2 D, 4 D, and a delayed reading on 6 D. Another patch test

was performed a month later. This time, he showed strong positive reactions to multiple corticosteroids on 4 D, again resembling an excited skin syndrome. The readings of patch test are summarized in Table 1. The International Contact Dermatitis Research Group grading scale was used (4).

The patch test reactions were consistent with his patch test results in 2000 and were believed clinically relevant. He was thought to have orally elicited ACD to corticosteroids, with the original sensitization being via the skin. Because corticosteroids are important emergency drugs, he was offered further evaluations, which would include patch tests with individual corticosteroids, PUT/ROAT, and oral provocation tests in order to identify a corticosteroid for future clinical use.

Comment

ACD to topical corticosteroids has a 3% incidence rate in positive reactions to tixocortol-21-pivalate, a 1.1% incidence rate for budesonide, and a 0.5% incidence rate for hydrocortisone-17-butyrate as reported by the North American Contact Dermatitis Group (5). Cross-reactions exist among topical corticosteroids (6). Sensitization to corticosteroids most commonly occur through skin, although other modes of sensitization such as orally, parenterally, or intralesionally do occur but are presumed less common (7). In sensitized individuals, a systemically administered allergen may occasionally reach the skin through the circulatory system and produce a maculopapular drug eruption (8). Patch tests, PUT/ROAT, and oral provocation tests (7) can elucidate the nature of orally elicited ACD to corticosteroids, especially for individu-

als who have had positive reactions to multiple corticosteroids.

The patch test procedure is a bioassay essential to a diagnosis of ACD. Skin hyperreactivity during diagnostic patch testing (excited skin syndrome) and its effect on the reliability of the test has been studied in detail (3).

In contrast, skin hyporeactivity or skin anergy during patch testing is poorly defined, oftentimes confusing, and infrequently described. Skin hyporeactivity describes a general state of diminished skin response to various challenges, both irritant and allergic, exogenous or endogenous, which exist not only in patients with obviously immunomodulated diseases but also in normal subjects, whereas skin anergy may be defined as a diminished skin reactivity/impaired cellular immune response to one or more specific antigens/allergens, as seen in sarcoidosis (1, 2) and cancer patients (9). Koehler and Maibach (2) suggested that skin hyporeactivity could be a cause of false-negative patch tests, which are clinically relevant and should not be overlooked. They also proposed the mechanisms of skin hyporeactivity, which might be the result of a faulty immune response or a defective inflammatory response, or both.

The negative patch test readings in our patient is a possible example that skin hyporeactivity exists, possibly because of an anergy state after a generalized orally elicited ACD to corticosteroid. It is possible that both the immune system and the inflammatory response are impaired. Unfortunately, the skin hyporeactivity occurred somewhat unexpectedly and we were unable to use the standardized irritant panel as a positive control (2) or to study the inflammatory biomarkers to validate the status of his skin. The nature of anergy in our patient has yet to be determined. The fact that he was

Table 1. Patch test results to corticosteroid series (6 weeks after discontinuing corticosteroid)

Corticosteroid		2 D	4 D
Budesonide	0.1% pet.	0	++~+++
Betamethasone-17-valerate	1.0% pet.	0	++~+++
Triamcinolone acetonide	1.0% pet.	0	++~+++
Tixocortol-21-pivalate	1.0% pet.	0	0
Alclometasone-17-21-dipropionate	1.0% pet.	0	++~+++
Clobetasol-17-propionate	1.0% pet.	0	++~+++
Dexamethasone-21-phosphate disodium salt	1.0% pet.	0	++~+++
Hydrocortisone-17-butyrate	1.0% alc.	0	++~+++

alc., alcohol.

again reactive to patch testing a month later suggested the transient nature of skin hyporeactivity/anergy in this individual.

Evidence-based data on how long systemically dosed corticosteroid remains in the skin and/or biologically active in skin have not been established. There are no data on prolonged patch test immunosuppression post-systemic corticosteroid. Hence, we have no recommendation as to when patch testing should be performed postsystemic corticosteroid. Detailed descriptions of the classification of corticosteroids and corticoid ACD are found in previous studies (6–8, 10–14).

The factors involved in the development, expression, and mitigation of dermatitis seem complex. The synergy of several factors involved in skin reactivity would explain the false-positive reactions as seen in excited skin syndrome or the false-negative reactions as a result of skin hyporeactivity as seen in our patient. However, most of the pathways and their contributions to skin reactivity remain unknown. Further studies and refined bioengineering methods are needed to clarify these phenomena.

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