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Follow your nose and keep an ear out: systemic dermatitis caused by prednisone derivatives in nose and ear drops

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Systemic dermatitis caused by corticosteroids may be underreported, and is likely to be the result of previous skin sensitization to the corticosteroid molecule involved (1). We present a case in which nose and ear drops were pinpointed as the specific allergen sources responsible for a recurrent, widespread skin eruption.

Case Report

A 40-year-old, non-atopic female patient was referred to us by her orthopaedic surgeon, by whom she was treated for a frozen shoulder, for the evaluation of suspected corticosteroid allergy. The patient reported the recent occurrence of an itchy maculopapular rash, originating in the main body folds, with subsequent involvement of the trunk, arms, and legs, without any systemic complaints. The history showed that the dermatitis had occurred approximately 2–3 days following treatment with a nasal spray (Sofrasolone[®]; Melisana Benelux NV, Brussels, Belgium), containing prednisolone acetate. Remarkably, neither skin lesions on the face or around the orifices (nostrils and nose) nor nasal congestion or rhinitis were present. The patient had experienced a very similar, generalized eruption several years ago following the use of ear drops, compounded by her local pharmacist, and containing, according to information that she could still retrieve from the pharmacist, either prednisolone or its derivative methylprednisolone. Also during that episode,

a rash had developed initially in the main body folds without any dermatitis of the ears. Furthermore, the patient recalled having had a localized skin reaction during childhood, with worsening of a pre-existent dermatitis, after applying a compounded pharmaceutical cream containing a corticosteroid whose name she could no longer remember. The surgeon, who was planning to treat her with methylprednisolone perorally (Medrol[®]; Pfizer, Brussels, Belgium), wanted to clarify (i) the existence of corticosteroid allergy, and (ii) safe alternative treatments that he could initiate.

Because of the suspicion of delayed hypersensitivity, patch tests were performed with a baseline series (containing three corticosteroid screeners: tixocortol-21-pivalate 0.1% in pet., budesonide 0.01% in pet., and hydrocortisone-17-butyrate 0.1% in ethanol), a cosmetic and pharmaceutical series, and a commercial corticosteroid series of molecules diluted 1% in pet. (betamethasone-17-valerate, triamcinolone-16 α -17-acetonide, alclomethasone-17,21-dipropionate, clobetasol-17-propionate, and dexamethasone-21-phosphate). A supplementary corticosteroid series prepared in-house of molecules diluted 1% in ethanol 96% (triamcinolone-16 α -17-acetonide, betamethasone-17,21-dipropionate, clobetasol-17-propionate, betamethasone-17-valerate, dexamethasone-21-phosphate, hydrocortisone-17-butyrate, and 6 α -methylprednisolone) was also tested. All commercially available tests were from Chemotechnique Diagnostics (Vellinge, Sweden), and patch test chambers were from Allergeaze[®] (Smartpractice[®], Phoenix, AZ, USA). The tests were fixed with Fixomull[®] stretch (BSN Medical GmbH, Hamburg, Germany), and occluded for 2 days, with readings being performed on day (D)2, D4, and D7.

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The reading at D7 showed ++ reactions to nickel and to methylisothiazolinone (MI) 2000 ppm (0.2%) aq., a + reaction to the mixture of MI and methylchlorisothiazolinone (MCI) 200 ppm (0.02%) aq., and a + reaction to methylprednisolone 1% in ethanol, with the early readings at D2 and D4 being completely negative for the last allergen. The three corticosteroid screeners of our baseline series and the corticosteroids diluted in pet. remained completely negative. The patient agreed to be patch tested again a few weeks later with some additional corticosteroids [methylprednisolone, this time at 0.1% in ethanol, prednisolone 0.1% in ethanol, hydrocortisone 0.5% in ethanol/dimethylsulfoxide (DMSO) (being an equal mixture of ethanol 96% and DMSO), betamethasone (unesterified) 0.1% in ethanol, triamcinolone-16 α -17-acetonide 0.1% in ethanol, and dexamethasone-21-phosphate 0.1% in ethanol]; this was in order to allow us to better define the culprit sensitizer(s) and to offer her alternative corticosteroids for treatment. These patch tests confirmed the reactivity to the prednisone derivatives prednisolone and methylprednisolone, and to the related group 1 corticosteroid hydrocortisone with, however, doubtful reactions (+?) already at D2 and clear positive reactions at D4 (Fig. 1), which were still present at D7. The tests with betamethasone, triamcinolone-16 α -17-acetonide and dexamethasone-21-phosphate gave negative results at all readings (Table 1). In order to definitely rule out contact allergy to triamcinolone-16 α -17-acetonide, the patient was tested a second time with much lower test concentrations of this corticosteroid (i.e. 0.01%, 0.001%, and 0.0001%, all in ethanol 96%), as recommended previously (2), but no reactions were observed at D2, D4, D7, or later.

The reactions to nickel and to the isothiazolinones (MI and MCI/MI) were not considered to be relevant for the drug eruptions that the patient had experienced,

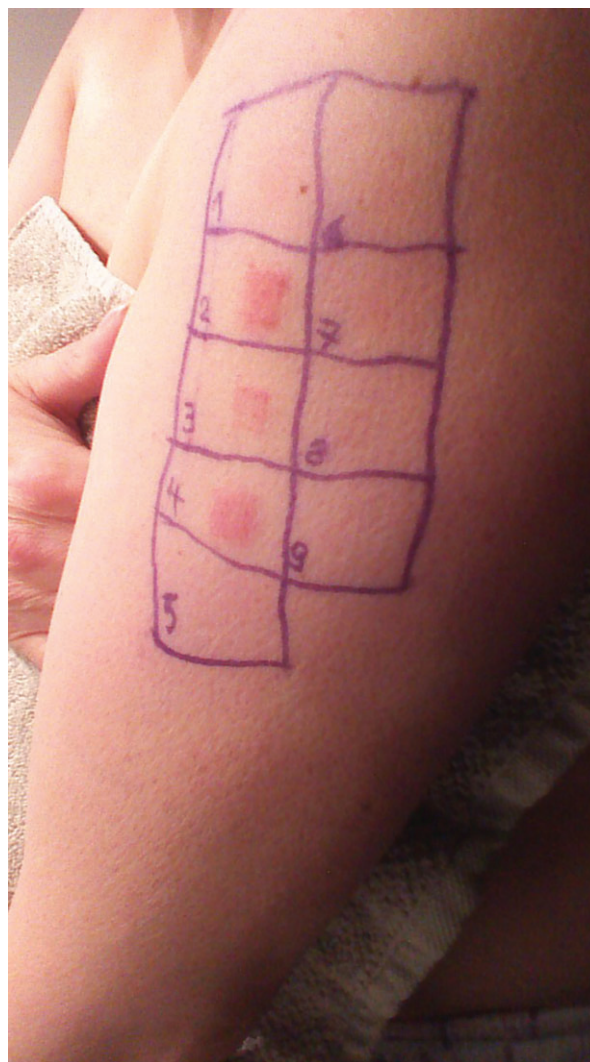


Fig. 1. Patch test reactions at D4 for: no. 2, methylprednisolone 0.1% in ethanol (++); no. 3, prednisolone 0.1% in ethanol (+); and no. 4, hydrocortisone 0.5% in ethanol/dimethylsulfoxide (++).

Table 1. Summary of relevant patch test results

Allergen	D2	D4	D7
Screeners*:			
Tixocortol-21-pivalate 0.1% pet., budesonide 0.01% pet., hydrocortisone-17-butyrate 0.1% eth.	–	–	–
Methylprednisolone 1% eth.	–	–	+
Methylprednisolone 0.1% eth.	?	+	++
Prednisolone 0.1% eth.	?	+	+
Hydrocortisone 0.5% eth./DMSO	?	+	++
Alternatives†:			
Triamcinoloneacetonide 0.1% eth., betamethasone 0.1% eth., dexamethasone 0.1% eth.	–	–	–
Ethanol (control)	–	–	–

eth., 96% ethanol; eth./DMSO, 50% ethanol 96%/50% dimethyl sulfoxide.

*Corticosteroid screeners in the Belgian baseline series.

†Alternative corticosteroids from corticosteroid groups 2 and 3.

but an MI-containing dishwashing liquid was later found by the patient as the most probable cause of a mild hand dermatitis. She was thus diagnosed with type IV allergy to corticosteroids from group 1, and triamcinolone-16 α -17-acetonide (group 2) and betamethasone (group 3) were shown to be possible safe alternatives. Triamcinolone-16 α -17-acetonide (Kenacort A10®; Bristol-Myers Squibb, Braine-l'Alleud, Belgium), dexamethasone (compounded by a pharmacist), and betamethasone (Celestone®; MSD, Brussels, Belgium), among others, are available in Belgium for systemic treatment, and the last of these was successfully administered to the patient, without any adverse events.

We hypothesize that, during childhood, the patient was sensitized topically to one of the prednisone derivatives (prednisolone or methylprednisolone), or to the potentially cross-reacting hydrocortisone, all three of which may be used in pharmacy-prepared therapeutic creams, especially for the treatment of (atopic) eczema of the face in children. A less likely sensitization route would have been the previous use of the compounded ear drops, containing either prednisolone or methylprednisolone, with the absence of any ear dermatitis pointing towards primary systemic sensitization, although this is considered to be uncommon (1). Other routes of sensitization were considered to be unlikely, given the history of our patient and the literature (3).

Discussion

Delayed hypersensitivity to corticosteroids is a well-known entity, and the prevalence varies between 0.2% and 5% among patients attending patch test clinics, with hydrocortisone, methylprednisolone and budesonide as the most reported culprit sensitizers (3). Several cases of allergic contact dermatitis following the use of corticosteroid-containing nasal sprays have been reported, with involvement of budesonide and tixocortol pivalate in particular (3–6).

Systemic dermatitis, on the other hand, may occur following systemic administration of corticosteroids, usually in a previously skin-sensitized patient, with the routes of exposure being mainly oral, intravenous, intramuscular, intra-articular and through the use of suppositories. In this subgroup of patients, methylprednisolone appears to be the most reported causal allergen (1).

Patch testing is considered to be the diagnostic method of choice for delayed hypersensitivity to corticosteroids, and delayed readings are required, owing to their anti-inflammatory properties. As the penetration

of corticosteroids when mixed in pet. is uncertain, they should always be tested in ethanol, with the exception of budesonide and tixocortol pivalate. Furthermore, the test concentrations are usually 1% (7), although 0.1% has been used as well (3), with the exception of hydrocortisone, which is better tested at 0.5% in ethanol/DMSO. When the higher concentration of 1% is used, the immunosuppressant effect of the corticosteroids prevails, with only late readings at D7 being positive, whereas the lower concentration of 0.1% might already give reactions at D2 and/or D4.

Interestingly, our three screeners for corticosteroid allergy, which are able to detect 92.5% of all corticosteroid contact allergies (3), were not sufficient for the diagnosis, with, in particular, tixocortol-21-pivalate failed to show reactivity for group 1 corticosteroids. Therefore, it is of utmost importance that the corticosteroids used by the patient are tested as well (3, 8, 9).

Corticosteroids showing cross-reactivity in patch testing and in clinical practice can be predicted with the recently revised classification of Baeck and Goossens, which consists of three groups of corticosteroids, and divides the corticosteroid-allergic patients into two profiles (10): profile 1 patients react to molecules from one group only, namely group 1, whereas profile 2 patients are capable of reacting to any of the corticosteroids. Most patients with systemic dermatitis seem to be profile 2 patients, for whom an individual approach is mandatory (1), implying patch tests with members of all three corticosteroid groups, in order to detect the cause of the skin eruption and to propose safe alternatives that can be used for a provocation test. Accordingly, negative patch test results were observed with both triamcinolone acetonide (group 2) and betamethasone (group 3), whereas the prednisone derivatives from group 1 were confirmed as the cause of the patient's recurrent eruptions. In the present case, it would appear that the patient was sensitized only to group 1, although we did not test an extensive corticoid series, as published elsewhere (3). Moreover, we exemplify here that the revised classification might also apply for systemically used corticosteroids.

In conclusion, this case shows that re-exposure to a corticosteroid in nasal sprays or ear drops, in individuals previously skin-sensitized to this corticosteroid or to a cross-reacting one, may result in a systemic dermatitis without the presence of concomitant skin lesions, that is, perinasal or ear dermatitis. Furthermore, we confirm that late readings of corticosteroid patch tests, especially with the 1% ethanolic dilutions, are of utmost importance, and that screening agents may sometimes be insufficient.

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