declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

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Allergic hypersensitivity to Deflazacort

To the Editor:

Corticosteroids are potent anti-inflammatories and immunomodulators used in the treatment of various inflammatory and allergic reactions that can cause delayed and immediate hypersensitivity, often misdiagnosed because of atypical clinical presentation.[1] There are four main groups (A, B, C and D with subgroups D1 and D2) defined by their chemical properties and depending on their molecular structure. Skin metabolism plays an important role in the allergenicity of corticosteroids and also influences the profile of cross-reactions.[2–3]

A 31-year-old-Caucasian female, lawyer, was assisted in the emergency room, after an exuberant swelling of her eyelid caused by an insect bite. She was treated initially with intravenous hydrocortisone and after discharge, with deflazacort (6 mg per day), clarithromycin and topical hydrocortisone. The patient returned to the emergency room 24 h later, for a widespread rash showing some individualised erythematous-pink plaques with circinate limits and pustules, interpreted as an urticarial reaction or as an acute exanthematous pustulosis.

She denied personal or family history of atopy, but reported an episode of acute dermatitis of the face caused by topical anti-acne cream, ten years before. Hypersensitivity to neomycin, tixocortol pivalate, Kathon CG, thimerosal, nickel, cobalt and benzoyl peroxide had been demonstrated in patch test performed that time.

The following immunoallergology tests were carried out: prick tests and intradermal tests with deflazacort 6 mg, hydrocortisone and clarithromycin in increasing dilutions. In addition, patch tests were performed with the basic series adopted by (PCDG), a corticosteroid series (including: dipropionate, betamethasone valerate, dexamethasone, triamcinolone, clobetasol, prednicarbat, mometasone, hydrocortisone and tixocortol pivalate), her own drugs and the other drugs already tested in immunoallergology.

Prick tests and intradermal tests: read for 20 min – negative. (immunoallergology). The first positive results were noted (by the patient) after 12 h: hydrocortisone and deflazacort 6 mg (Fig. 1, Table 1).

Hypersensitivity was shown to tixocortol pivalate (a Group A substance), as well as to hydrocortisone (Group A)

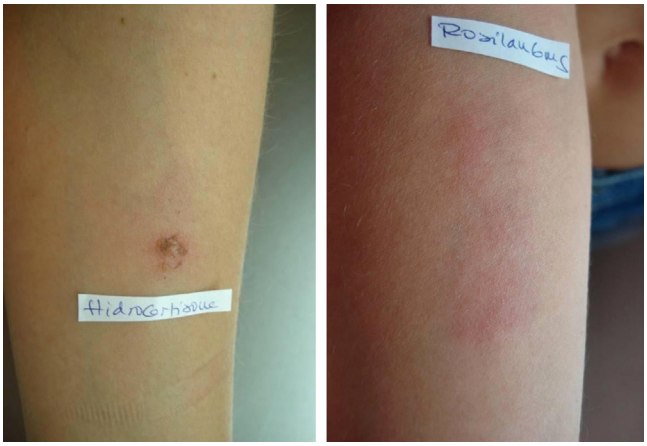

Figure 1 Reading of intradermal tests at 48 h.

Table 1 Reading of prick tests and intradermal tests.

Prick tests and intradermal tests	48 h	96 h
Hydrocortisone	++	++
Deflazacort 6 mg	++	++

Table 2 Evidence from reading patch tests with the basic series adopted by PCDG, corticosteroids and the patient's own drugs in increasing dilutions.

Patch tests (epicutaneous test)			
Basic series	48 h	96 h	1st week
Nickel sulphate 5% pet	+	+	-
Cobalt chloride 1% pet	+	++	-
Budesonide 5% pet	N	N	N
17 hydrocortisone butyrate 0.1% pet	N	N	N
Corticosteroid series	48 h	96 h	1st week
Deflazacort 30 mg 30% pet	—	++	+
Hydrocortisone 12.5% pet	—	+	+
Tixocortol pivalate 0.1% pet	++	+++	+++
Deflazacort 6 mg as such	++	+++	++
Deflazacort 6 mg 1/1000 s	+	++	++
Deflazacort 6 mg 1/10 s	+	++	+
Deflazacort 30 mg as such	++	+++	++

and deflazacort. They have a similar structure to methylprednisolone (which also belongs to Group A) (Table 2).

As an option to find alternative therapies, we proceeded to prick, intradermal tests and patch test with methylprednisolone, dexamethasone sodium phosphate, betamethasone and prednisolone in increasing dilutions: as such, 1/10, 1/100, 1/1000 in saline.

Positive readings were obtained 12 h after the intradermal tests were started (prednisolone and methylprednisolone), while the patch tests were negative (Table 3).

The prevalence of allergy to corticosteroids is highly variable: contact allergic reactions occur in 0.2 to 5% of patients who undergo patch tests while the immediate hypersensitivity is rare, representing 0.1–0.3%.[4]

Allergic reactions may also arise from systemic administration, although the prevalence is not known.[4] The published cases of reaction to deflazacort are rare.[5–6]

Table 3 Evidence from reading prick tests and intradermal tests with corticosteroids in increasing dilutions given by systemic administration.

Prick tests and intradermal tests	48 h	96 h	1st week
Methylprednisolone 40 mg *(as such)*	++	+	+
Methylprednisolone 1/10 s	++	+	+
Methylprednisolone 1/100 s	++	+	+
Methylprednisolone 1/1000 s	++	+	+
Prednisolone 1/10 s	++	+	+
Prednisolone 1/100 s	++	+	+
Prednisolone 1/1000 s	++	+	+

Deflazacort is a derivative component of prednisolone, given by oral intake and widely used because of its minimal adverse effects. It has a similar structure to methylprednisolone, with a connection with oxazoline in C17.[5] Some authors believe that it does not cross-react with other corticosteroids.[7]

Corticosteroids are classified into four groups, depending on their molecular structure and chemical properties. Cross-reactions occur mainly between corticosteroids within the same group, while the cross-reactions between groups are not frequent.[7]

Tixocortol pivalate is involved in almost 90% of type IV reactions.[4]

In the case of this patient, hypersensitivity to tixocortol pivalate (marker of Group A), found in tests carried out 10 years before, irrelevant at that time, can be considered premonitory of the later reaction to deflazacort. Intradermal tests were positive at 48 h and 96 h readings for hydrocortisone, which also belongs to group A, as well as for deflazacort 6 mg in different dilutions. The epicutaneous tests confirmed hypersensitivity to tixocortol pivalate in vaseline, to hydrocortisone (also in vaseline) and increasing dilutions in saline, as well as to deflazacort 6 mg. Although the preparation of active ingredients in ethanol is being indicated,[4] it was not practically feasible to carry out those tests.

Intradermal tests become positive earlier than the patch tests. The results from both tests were in agreement most of the time,[4] as occurs in this case.

It can be assumed that the clinical evolution was a response comparable to the one reproduced during testing (delayed reaction).

The results obtained with the prick and intradermal tests with commercial preparations of systemic administration (methylprednisolone, dexamethasone, sodium phosphate, betamethasone and prednisolone) confirmed hypersensitivity to methylprednisolone and prednisolone, both in Group A. These tests may be extremely helpful, finding alternative drugs that may play a vital role for the patients, which in this case was dexamethasone.

The metabolism of corticosteroids in the skin can also lead to cross-reactions between classes, if the molecules behave as haptens before and after bio-metabolisation.[2–5] Deflazacort and methylprednisolone (Group A) share structural similarity, which may explain a cross or concomitant reaction.

Soria et al.[4] advocate that patch tests with the active ingredients diluted in ethanol are the preferred diagnostic method for delayed hypersensitivity to corticosteroids. Intradermal tests with delayed readings can detect additional cases. However, they should not be performed routinely because of the risk of atrophy.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this investigation.

Patients' data protection. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

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Hypersensitivity pneumonitis caused by metalworking fluid

To the Editor,

Metalworking fluids (MWF) or cutting oils have been recognised as causes of work-related respiratory problems.[1] Most workers who are affected by these problems are employees of the automotive industry.

Case reports of occupational asthma (OA) due to MWF have been reported previously.[2,3]

The first cases of alveolitis due to MWF were reported by Bernstein et al., who described six cases of hypersensitivity pneumonitis.[4] In some cases included in this study precipitating antibodies to a number of microbial isolates were found, the most common being *Pseudomonas fluorescens*. Other outbreaks[5,6] are thought to have been caused by bacterial (particularly mycobacteria) or fungal contamination of MWF, but no specific agent has fulfilled the criteria for a specific cause. A more recent report[7] described 12 workers who produced heterogeneous clinical, radiological and pathological findings, but all met the case definition for HP. Only one worker with suspected HP was challenged with used and clean MWF, exhibiting a late reaction only when exposed to the used fluid.[8] It was therefore confirmed that the chemical constituents alone were unlikely to have caused the disease; rather, the contaminated MWF was the cause of the disease in most cases.

We report a 30-year-old male non-smoker who developed recurrent episodes of malaise and shortness of breath related with his job. In his workplace, metallic parts were cut using MWF. As a part of the process used, the fluid is heated, producing aerosol. The product labelling and material safety data sheet showed that the substance contains aminoethanol and other unspecified products. The man had worked in the same job for ten years. He did not use a protective mask at work. He had a previous diagnosis of mild seasonal allergic rhinoconjunctivitis. Following a one-month sick leave, the patient was symptom-free. Two months after the sick leave, a CT scan was reported as normal and spirometry revealed FVC of 66% and FEV1 of 77%. Three months later the patient was referred to our unit. At this time, spirometry was normal, as was the fraction of exhaled nitric oxide. A methacholine inhalation test revealed no airway hyperresponsiveness (PC20 > 16 mg/ml) and diffusing capacity was normal (DL_{CO} 98%). The MWF he used during the symptomatic phase was submitted for microbacterial analysis of possible bacteria and mycobacteria. All cultures yielded negative results. After signing an informed consent a specific inhalation challenge with an MWF that was of the same brand but new was performed by heating the product. The patient was exposed to a concentration of 0.87 mg/m^3 (DustTrack model 8520, TSI, St. Paul, MN, USA) for 30 min in a closed chamber for exposure to particles and fumes.[9] Clinical symptoms and body temperature were monitored hourly until bedtime, and spirometry measurements were taken using a portable electronic spirometer (Amos, Jaeger, Germany). He presented a late (eight hours) fall of FVC of 15%. Twenty-four hours after this challenge diffusing capacity and lung volumes did not change, and neither did the haemogram. The next day the patient was exposed to the MWF for two hours while inside the chamber. Seven hours after the exposure was concluded, and over a duration of three hours, he presented with malaise, up to 37.5 °C, shortness of breath and a fall of FVC of 17%. Twenty-four hours after the second challenge diffusing capacity and haemogram did not change although there was an increase of residual volume to 158%.

There is no single specific radiological, physiological, or immunological test suitable for the diagnosis of hypersensitivity pneumonitis,[10] but changes in body temperature and FVC are predicting values of chronic HP.[11,12] The bronchial challenge test in this case showed significant late drop in FVC and an increase in residual volume suggestive of a peripheral lung reaction together with a rise in body temperature. Therefore, the results of the clinical symptoms and challenge test in this worker strongly suggest that he had developed hypersensitivity