Case Report

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Oral Prednisolone Induced Acute Generalized Exanthematous Pustulosis due to Corticosteroids of Group A Confirmed by Epicutaneous Testing and Lymphocyte Transformation Tests

U. Buettiker[a] M. Keller[b] W.J. Pichler[b] L.R. Braathen[a] N. Yawalkar[a]

[a]Department of Dermatology and [b]Clinic for Rheumatology and Clinical Immunology/Allergology, Inselspital, University of Berne, Berne, Switzerland

Key Words
Acute generalized exanthematous pustulosis · Pustulosis · Prednisolone · Patch test · Lymphocyte transformation test

Abstract
Background: Acute generalized exanthematous pustulosis (AGEP) is a rare cutaneous eruption which is often provoked by drugs. ***Case Report:*** We report 2 cases of AGEP which showed rapidly spreading pustular eruptions accompanied by malaise, fever and neutrophilia after the administration of systemic prednisolone (corticosteroid of group A, hydrocortisone type). The histological examination showing neutrophilic subcorneal spongiform pustules was consistent with the diagnosis of AGEP. In both cases the rash cleared within a week upon treatment with topical steroids (corticosteroid of group D1, betamethasonedipropionate type and corticosteroid of group D2, hydrocortisone-17-butyrate type). Three months after recovery, the sensitization to corticosteroids of group A was confirmed by epicutaneous testing and positive lymphocyte transformation tests. ***Conclusion:*** These cases show that systemic corticosteroids can induce AGEP and demonstrate that epicutaneous testing and lymphocyte transformation tests may be helpful in identifying the causative drug. Our data support previous reports indicating an important role for drug-specific T cells in inducing neutrophil inflammation in this disease.

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare entity which is characterized by the acute formation of multiple, small, mostly nonfollicular, sterile pustules on an erythematous base and is accompanied by fever and leukocytosis (i.e. neutrophilia) [1, 2]. The histopathological findings include subcorneal or intraepidermal spongiform pustules with a variable degree of dermal edema, vasculitis, perivascular eosinophils and focal necrosis of individual keratinocytes. Drugs (in particular antibiotics) are the most likely cause of AGEP, accounting for approximately 90% of all cases. The mortality rate of AGEP has been reported to be approximately 2% [1, 3]. Therefore, the identification and prompt removal of the culprit drug are important. Here we report 2 cases of AGEP elicited by corticosteroids of group A (hydrocortisone type), which were confirmed by positive patch tests and a lymphocyte transformation test (LTT).

Case Report 1

A 42-year-old man (patient A) suffering from perianal eczema was initially treated for 3 weeks with topical prednisolone acetate cream (corticosteroid of group A, hydrocortisone type). Due to the aggravation of this eczema, the patient was subsequently given systemic treatment with 50 mg prednisolone followed by 100 mg prednisolone tetrahydrophthalate (both corticosteroids of group A, hydrocortisone type). Some hours after receiving prednisolone tetrahydrophthalate, the patient developed an erythematous rash with subsequent occurrence of numerous nonfollicular pustules on the trunk and the extremities over the following days. The exanthem was associated with burning, pruritus as well as malaise and fever (temperature of 38°C). No mucosal involvement was noted. The family and personal history were negative for psoriasis or atopy, and the patient was on no other medication. The laboratory investigations showed leukocytosis (17.1·

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Nikhil Yawalkar, MD
Department of Dermatology
Inselspital
CH–3010 Berne (Switzerland)
Tel. +41 31 632 80 42, Fax +41 31 632 05 55, E-Mail nikhil.yawalkar@insel.ch

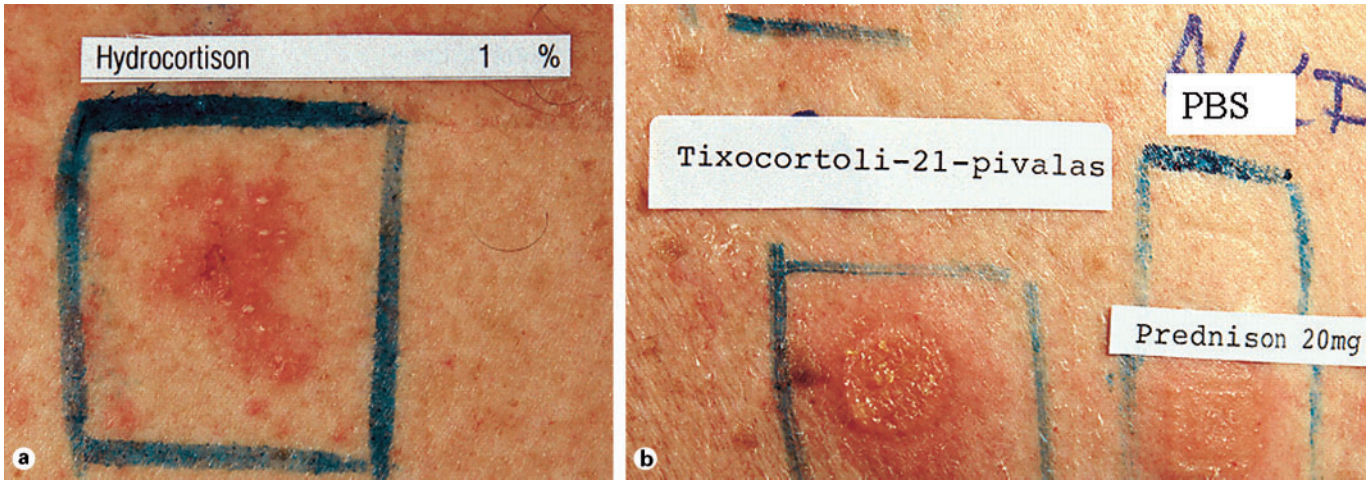

Fig. 1. A positive reaction for hydrocortisone 1% (**a**) and prednisone, prednisolone 1%, tixocortol pivalate 1% (**b**) (all group A, hydrocortisone type) in patient B. Note the presence of pustules in **a**.

Table 1. Summary of positive test results

	Patch test	LTT
Patient A		
Corticosteroids of group A		
Prednisone	pos.	neg.
Prednisolone	neg.	pos.
Hydrocortisone	neg.	pos.
Patient B		
Corticosteroids of group A		
Prednisone	pos.	pos.
Prednisolone	pos.	neg.
Hydrocortisone	pos.	n.d.
Hydrocortisone acetate	n.d.	pos.
Tixocortol pivalate	pos.	n.d.
Corticosteroids of group B/D2		
Budenoside	pos.	neg.

n.d. = Not done.

10^9 l^{-1} with 55.1% segmented neutrophils, 36.4% band neutrophils, 5.4% lymphocytes and 0.05% eosinophils), elevated C-reactive protein (187 mg l^{-1}) and normal renal and liver function tests. The bacterial cultures from a pustule, the blood and the urine were all negative. The histological examination revealed subcorneal spongiform pustules with some dermal edema as well as a dense perivascular and interstitial inflammatory infiltrate with lymphocytes, neutrophils and scattered eosinophils. The patient was diagnosed as having AGEP and was treated with mometasone furoate cream (corticosteroid of group D1, betamethasone dipropionate type), which led to recovery within a week.

Case Report 2

A 58-year-old man (patient B) suffering from chronic polyposis had received treatment with triamcinolone acetonide suspension (corticosteroid of group B, triamcinolone acetonide type). Due to further aggravation he was given a single oral dose of 60 mg prednisolone (group A, hydrocortisone type). Some hours later he presented a widespread erythema with burning, pruritus, malaise and fever (temperature of 38.5°C) and subsequently developed numerous, small, nonfollicular pustules on the trunk, the extremities and the scalp. There was no mucosal involvement. His personal history revealed an atopic and seborrheic eczema, which had been treated with topical prednisolone and hydrocortisone acetate cream (corticosteroid of group A, hydrocortisone type) and halometasone cream (corticosteroid of group C, betamethasone type nonesterified). His past and family history were negative for psoriasis.

The laboratory investigations showed neutrophilia ($8.15 \cdot 10^9$ l^{-1}), elevated C-reactive protein (50 mg l^{-1}) and normal renal and liver function tests. The bacterial cultures from a pustule, the blood and the urine were all negative. The histological examination showing neutrophilic subcorneal spongiform pustules was consistent with the diagnosis of AGEP. The patient was treated with hydrocortisone butyrate cream (corticosteroid of group D2, hydrocortisone-17-butyrate type) and recovered within a week.

Skin Tests

Three months after recovery patch tests were performed with prednisone (20 mg/0.2 ml PBS), dexamethasone (4 mg/0.2 ml PBS) and PBS (negative control) as well as with a commercially available corticosteroid series (Hermal, Reinbek, Germany) including amcinonide 0.1%, betamethasone-17-valerate 0.12%, budesonide 0.1%, clobetasole-17-propionate 0.25%, hydrocortisone 1%, hydrocortisone-17-butyrate 0.1%, triamcinolone acetonide 0.1%, prednisolone 1%, tixocortol pivalate 1% and Vaseline (negative control) as described previously [4]. Patch tests were performed on the upper back of the patients and read after 48–120 h. A summary of the positive test results is shown in table 1. Patient A revealed a positive reaction to prednisone, demonstrating a sensitization exclusively to the corticosteroids of group A (hydrocortisone type). As illustrated in figure 1, a positive reaction to hydrocortisone 1%, prednisone 20 mg, prednisolone 1%, tixocortol

pivalate 1% (all corticosteroids of group A, hydrocortisone type) as well as for budesonide 0.1% (corticosteroid of group B, triamcinolone acetonide type) was found in patient B.

Lymphocyte Transformation Test

Three months after recovery an LTT with hydrocortisone, hydrocortisone acetate, prednisolone, budesonide and tetanus (positive control) was performed with heparinized blood of the patients as previously described in detail [5]. Briefly, peripheral blood mononuclear cells were isolated using standard Ficoll-Hypaque (Pharmacia, Uppsala, Sweden) density gradient centrifugation. Cell cultures were set up with the drugs (1, 10 and 100 μg ml^{-1}) in 0.2 ml of RPMI 1640 supplemented with 20% AB serum. After 5–6 days ^{3}H-thymidine (0.5 mCi) was added for 14 h, the cultures were harvested and the counts per minute were measured in a β-counter (Packard, Canberra Corp., Meriden, Conn., USA). The ^{3}H-thymidine uptake measured, it was expressed as a stimulation index (SI), which is defined as the quotient of the measurement with antigen and the control without antigen. An SI above 2.0 was considered to be significant.

In both patients a significant proliferation (^{3}H-thymidine incorporation) of T cells to hydrocortisone and to prednisolone was detected as compared to the negative control (medium), again confirming a T cell sensitization to corticosteroids of group A (hydrocortisone type). As shown in figure 2, the SI for hydrocortisone (at 1 and 10 μg ml^{-1}) in patient A was 3.4 and 4.0, respectively, and a slightly positive stimulation (SI 2.1) was also found for prednisolone (at 10 μg ml^{-1}). As demonstrated in figure 3, the SI for prednisone (at 1 and 10 μg ml^{-1}) in patient B was 5.2 and 6.3, respectively. A positive SI (2.5 and 2.3) was also seen for hydrocortisone acetate (at 1 and 10 μg ml^{-1}, respectively) in this patient. The control lymphocyte proliferation assays with hydrocortisone, hydrocortisone acetate and prednisolone were negative in nonsensitized individuals, confirming the specificity of the LTT.

Provocation Tests

After an allergological workup a provocation test with oral betamethasone (corticosteroid of group C, betamethasone type nonesterified) was performed in both patients. This provocation test was well tolerated by patient A. Interestingly, patient B developed a maculopapular rash on the trunk 2 days after the provocation with this corticosteroid of group C, which cleared upon treatment with pimecrolimus cream. Subsequently, the patient was given oral dexamethasone (another corticosteroid of group C), which was then tolerated.

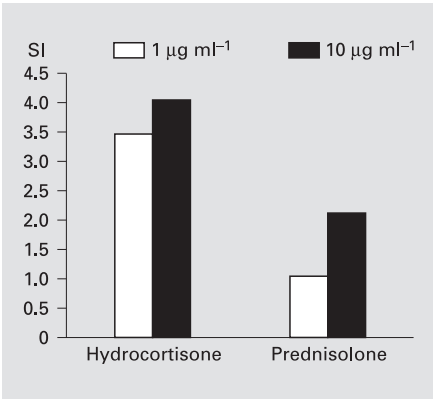

Fig. 2. A significant lymphocyte stimulation (SI 3.4/4.0) for hydrocortisone (1 and 10 μg ml^{-1}, respectively) and a slight stimulation (SI 2.1) for prednisolone (10 μg ml^{-1}) were observed in patient A.

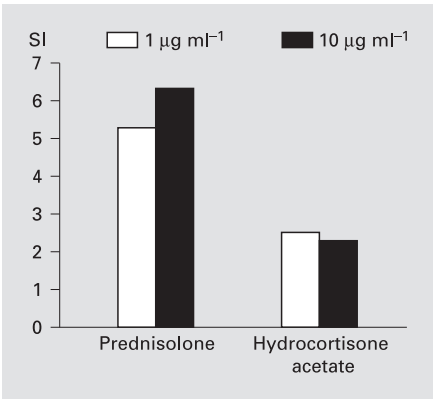

Fig. 3. A significant lymphocyte stimulation (SI 5.2/6.3) was found for prednisone (1 and 10 μg ml^{-1}, respectively) in patient B. A positive SI (2.5 and 2.3) was also seen for hydrocortisone acetate (at 1 and 10 μg ml^{-1}, respectively) in this patient.

Discussion

Based on the clinical and histological features as well as the allergological workup, our patients suffered from AGEP elicited by corticosteroids of group A (hydrocortisone type). In recent years corticosteroids have been reported to elicit a variety of adverse drug reactions. Contact hypersensitivity is the most common form with an overall frequency of positive patch test reactions of 2.6% to certain corticosteroids [6]. Based on the substitution of the D ring and certain cross-reactivity patterns in patch tests, 4 groups (A–D) of structurally related corticosteroids have been classified [7]. These include group A (hydrocortisone type), group B (triamcinolone acetonide type), group C (β-methasone type nonesterified) and group D (esters). The latter group can now be subclassified into 2 groups, i.e. group D1 (betamethasonedipropionate type) and group D2 (hydrocortisone-17-butyrate type) [8].

In contrast to contact dermatitis, generalized delayed-type hypersensitivity reactions after the systemic administration of corticosteroids are quite rare [9]. The clinical features of these reactions are most often generalized erythema, macularpapular exanthem and widespread eczema. Prednisolone and its derivatives (corticosteroids of group A, hydrocortisone type) have frequently been identified as the causative agents [9]. So far only 2 cases of AGEP elicited by corticosteroids (methylprednisolone, dexamethasone) and confirmed by positive patch test results have been published [10, 11]. However, the proof that corticosteroids are the causative drug is difficult due to their inherent immunosuppressive properties. Since corticosteroids are widely used due to their anti-inflammatory and immunoregulatory effects, the appropriate identification of an allergy to corticosteroids and the performance of provocation tests to determine safe alternatives are mandatory. Furthermore, AGEP may develop into a severe adverse drug eruption, which is potentially life threatening, especially for older patients [1, 3]. Therefore, reexposure to the suspected drug is not feasible, and alternative tests to identify drug allergy are necessary. The sensitivity of patch testing to drugs in AGEP has been reported to be approximately 50% [12, 13]. Previous reports have indicated that the LTT may be helpful in determining drug allergy in AGEP despite negative skin test-

ing [14–17]. To our knowledge a significant lymphocyte stimulation to corticosteroids has not been reported previously in AGEP. Our data demonstrate that this assay may indeed be useful in identifying the causative drug, even in the case of corticosteroids.

The positive epicutaneous and lymphocyte transformation test results provide further evidence for a key role of drugspecific T cells in AGEP. Previous reports indicate that both drugspecific, cytotoxic CD4+ and CD8+ T cells are primarily activated and lead to vesicle formation in the epidermis [18, 19]. The subsequent release of pro-inflammatory cytokines und chemokines such as IL-8 /CXCR8 by CD4+ T cells and resident cells, i.e. keratinocytes, is thought to lead to the recruitment of neutrophils and pustule formation. Recently, a novel subclassification of delayed-type IV hypersensitivity reaction has been proposed. It divides this reaction into 4 subtypes (types IV a–d) according to the cytokine profile and function (i.e. cytotoxicity) of the T cells involved [20]. Taking this subclassification into account, AGEP may represent a peculiar type of a delayed hypersensitivity reaction, where cytotoxic T cells (type IV c) and T cells producing large amounts of certain cytokines and chemokines (IL-8/CXCR8), which preferentially activate and recruit neutrophils (type IV d), are predominantly activated.

Taken together, our cases demonstrate that systemic corticosteroids may elicit AGEP and that the corticosteroids involved may be identified by skin tests and in vitro tests. An awareness of the different groups (A–D1/D2) of corticosteroids with regard to allergic reactions and an appropriate allergological workup are mandatory in these patients.

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