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UV-A-provoked Localized Bullous Pemphigoid

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A 71-year-old woman had noticed the development of blisters on her forehead 4 months before she was referred to our department. Treatment with oral corticosteroids resulted in complete healing, but new blisters subsequently developed on the face, neck and backs of the hands. After the possibility of phototoxic and photoallergic reactions, as well as an abnormal porphyrin profile, had been excluded, the diagnosis of bullous pemphigoid was made by histological and direct immunofluorescent examination. UV-A provocation on the upper arm produced lesions histologically and immunohistochemically typical of bullous pemphigoid. Of particular importance was the fact that the blisters were limited strictly to light-exposed skin areas. ***Key word: light-exposed skin areas.***

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The disease known as bullous pemphigoid, first described by Lever in 1953, is characterized by the formation of bullae at the dermo-epidermal junction (1). In addition to normal bullous and cicatricial pemphigoid, some other rare variants have been described, including vesicular, vegetating, hyperkeratotic-scarring, dyshidrosiform and erythematous pemphigoid. Localized forms of bullous pemphigoid are known, the most common sites for these being the lower extremities (2–5).

Although the exact etiology is still unknown, current research suggests an autoimmune genesis as a potential cause. In approximately 70% of patients, pemphigoid antibodies belonging to the IgG class, mainly the subtypes IgG4 and IgG1, can be detected by indirect immunofluorescence. Deposition of IgG and C3 in the basal membrane zone can be seen in direct immunofluorescence (6). The mechanism of blister formation is understood as a reaction of circulating autoantibodies to an antigen which is not, as previously thought, located at the lamina lucida, but in and around hemidesmosomes of the basal cells. More than one antigen seems to be involved (molecular weight 220–240 kD and 166–180 kD) (7–11). This is followed by activation of complement, chemotaxis of neutrophils and eosinophils and release of enzymes (12). Besides the autoimmune genesis, triggering of bullous pemphigoid can also result from taking certain drugs (e.g. salazosulfapyridine, penicillin, furosemide, diazepam, captopril) or can be induced by X-rays, injuries, PUVA therapy and UV light (13–15, 21). The role of bullous pemphigoid as a paraneoplastic syndrome is controversial. Contrary to what was formerly believed, the incidence of internal malignancies in all patients with bullous pemphigoid does not seem to be higher (4, 22, 23). This report describes a patient with blisters limited to light-exposed skin areas which were provoked by exposure to UV light following history and UV provocation testing.

CASE REPORT

A 71-year-old patient had noticed blistering on her forehead that became increasingly severe over a period of 4 months and spread over the face, neck, forearms, and backs of the hands. The condition was accompanied by severe itching, and the patient observed that exposure to sunlight led to deterioration. Treatment with oral corticosteroids resulted in temporary healing, followed, however, by the recurrence of blisters after medication had been discontinued.

In September 1992 the patient was referred to our department. She had been treated for diabetes mellitus for 3 years with glibenclamide and for cardiac insufficiency with captopril, hydrochlorothiazide and metildigoxin. In addition to the occasional taking of oxazepam, the regular use of an artificial sweetener (cyclamate sodium, saccharin) was also reported.

Examination of the skin revealed that only light-exposed skin areas such as face, ears, neck, and backs of the hands were affected. On the face, a diffuse erythema with slight edema and fine scaling was noted. On the forehead, multiple erosions could be seen, partly covered by hemorrhagic crusts (Fig. 1), whereas in the neck area, only a diffuse erythema with slight edema was present. The backs of the hands showed tense blisters on erythematous plaques with clear fluid content in addition to several erosions (Fig. 2). Nikolski phenomenon I and II were negative. The results of the physical examination were normal. Several bacteriological smear preparations taken from the blister content were positive for coagulase-negative *Staphylococcus, Acinetobacter, Staphylococcus aureus* and *Pseudomonas aeruginosa.* Ultrasound of the abdomen revealed only a single small gall-stone and a calcification in the uterus. X-ray examination of the chest and ECG were normal.

Testing of the minimal erythema dose (MED) showed a normal MED range (28 J/cm^2 for UV-A and 112 mJ/cm^2 for UV-B), but a persistent erythema in the UV-A-exposed area was noted even 5 days after irradiation as evidence for a pathological light reaction. Provocation testing with UV-A (100 J/cm^2 applied three times at intervals of 24 h) led to eruption of blisters in the irradiated area. The same procedure performed with UV-B (150 mJ/cm^2) had no pathological result. The photopatch test was positive for 1-(4-isopropylphenyl)-3-phenyl-1,3-propandion 4-isopropyldibenzoylmethan, a substance contained in numerous topical sunscreens. Test results for hydrochlorothiazide, captopril and glibenclamide were negative.

In two samples of tissue taken from the back of the left hand and forehead (routinely H&E-stained) there was a subepidermal blister containing little fluid, fibrinous fibrils and some eosinophils and neutrophils. The surrounding epidermis showed slight exocytosis of eosinophils. In the upper dermis, a perivascular infiltration consisting of lymphocytes, neutrophilic leucocytes and some eosinophils was seen. A sample of a blister taken from the right upper arm after irradiation with UV-A showed similar histological changes. With direct immunofluorescence, deposits of IgG and C3 could be found in the region of the lamina lucida of the basement membrane of all three tissue samples.

The routine laboratory findings were normal; only the blood glucose level was moderately raised. Ds-DNA, ANA, antibodies against intercellular components, antibodies against endomysium and Sm antigen, lipoproteins Ro (SS-A) and La (SS-B), extractable ribonucleoproteins, ASL, electrophoresis and immunoelectrophoresis were either

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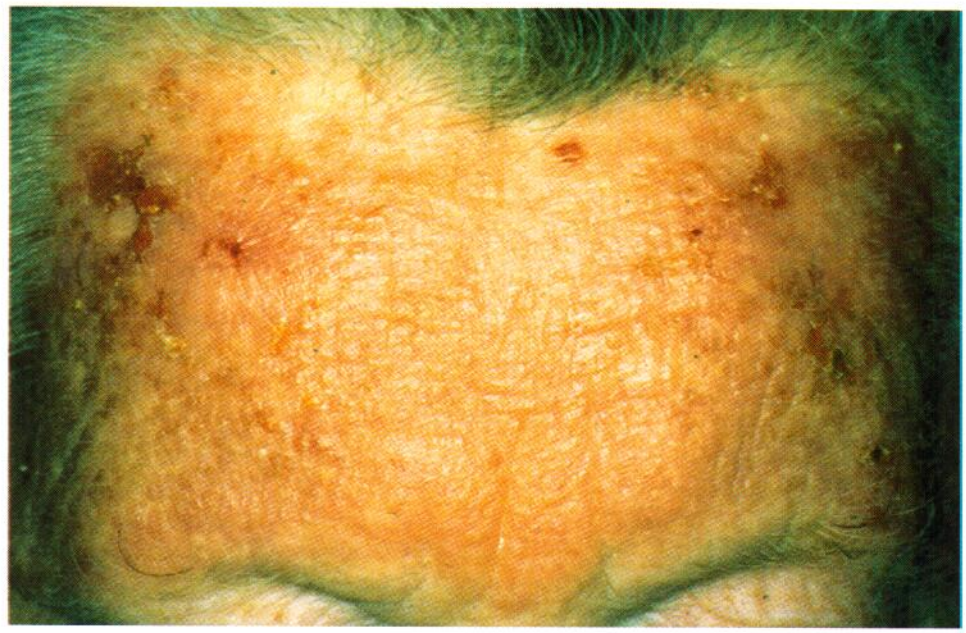

Fig. 1. Close-up view of the forehead: multiple erosions partly covered by hemorrhagic crusts.

negative or normal. The porphyrin profile in erythrocytes, urine, and stool was also normal. Anti-basement membrane zone antibodies could not be detected by indirect immunfluorescence technique.

After admission of the patient to our department, a phototoxic or photoallergic reaction was initially considered and the possibly photosensitizing medications were changed or discontinued (hydrochlorothiazide, captopril, glibenclamide). Sunscreens containing 1-(4-isopropylphenyl)-3-phenyl-1,3-propandion 4-isopropyldibenzoylmethan were avoided. Local treatment with prednicarbate cream, astringents and gentamicin cream was started. Nevertheless, there was a continuous eruption of new blisters. Under treatment with oral corticosteroids (methylprednisolone 40 mg for 3 days, then reduction) the patient developed no new bullae. However, one day after the treatment had been discontinued, new lesions appeared, thus requiring resumption of methylprednisolone. After discharge of the patient, the first efforts to discontinue the treatment promptly resulted in a relapse, but there was a successful gradual reduction and complete withdrawal trial 4 months later. During a follow-up period of 6 months no recurrence was observed.

DISCUSSION

The skin lesions of our patient corresponded most likely to bullous pemphigoid. The fact that blistering was strictly limited to light-exposed skin areas was unusual. As a differential diagnosis, a phototoxic or photoallergic reaction was also considered. The medication taken by the patient included hydrochlorothiazide, a substance which can trigger photosensibilization. This phenomenon has been reported with captopril and glibenclamide as well and is also true of artificial sweeteners which were used by the patient. The result of the histological examina-

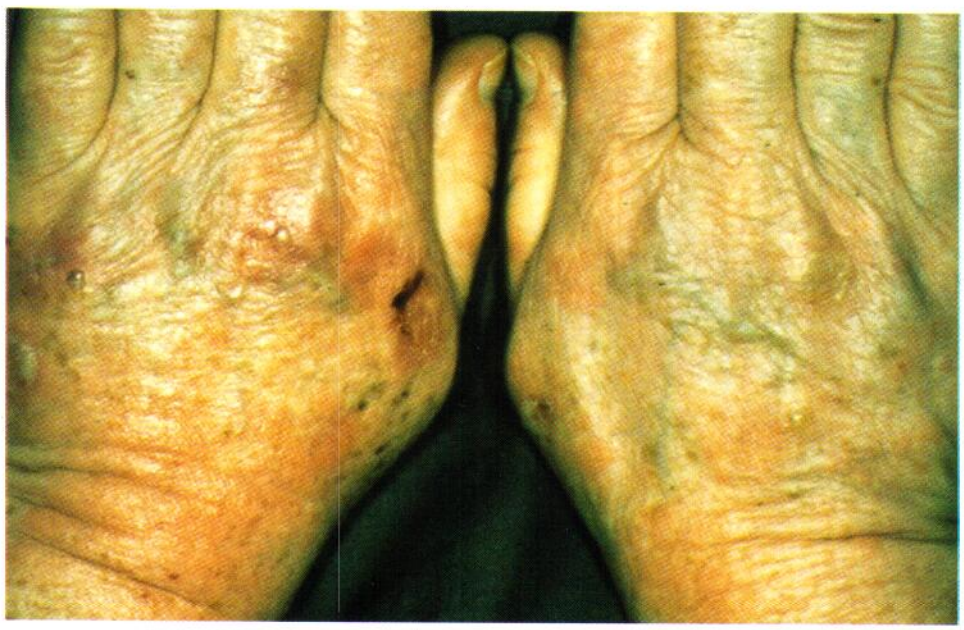

Fig. 2. Tense blisters on erythematous plaques with clear fluid content and several erosions.

tion, however, was not compatible with a phototoxic or photoallergic reaction: there were no epidermal spongiosis, dermal edema and enlargement of endothelial cells; typical sunburn cells (vacuolated keratinocytes) were missing; and blister formation was subepidermal instead of spongiotic intraepidermal blisters as might be expected. And since discontinuing or changing the medication for an adequate period of time had no influence on the disease, these substances could be ruled out as provocating factors. Porphyria was excluded by histological results and a normal porphyrin profile.

Based on the typical histological changes – subepidermal blister with eosinophils, neutrophils and threads of fibrin, perivascular inflammatory cell infiltrate with eosinophils, and the characteristic IgG and C3 deposits in the basal membrane zone with direct immunofluorescence – we established the diagnosis of bullous pemphigoid.

Medical examinations showed no sign of internal malignancy and thus no evidence for paraneoplastic bullous pemphigoid. The strict limitation of the blisters to the face, neck, forearms, and backs of the hands draws attention to the role of light as the provocation factor. This was supported by the history (deterioration after sun exposure). Besides a pathological reaction to UV-A when the MED was tested, typical blisters could also be provoked by irradiation with UV-A. Some reports on UV- or sunlight-induced bullous pemphigoid have been published (15, 20, 21). There is also a report on UV-B induced bullous pemphigoid that was restricted to the plaques of mycosis fungoides (24). The limitation of blister eruption to sun-exposed skin areas, as described in this case, is not typical of bullous pemphigoid and has only been described in one report, where lesions appeared on the patient's nose after sunbathing (20).

For our patient, UV-A light seems to be the responsible stimulus which – as proposed by Jordon et al. – converts the bullous pemphigoid antigen into an immunogenic signal. This is followed by synthesis of IgG antibodies which bind to the bullous pemphigoid antigen. This in turn sets off the production and activation of inflammatory mediators (25). However, this phenomenon seems to occur only in sun-exposed skin areas.

Treatment with oral corticosteroids in conjunction with the use of topical sunscreens has led to a suppression of the disease. In case of a relapse, the treatment with corticosteroids will be continued or a combination of corticosteroids and azathioprine will be tried.

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