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Photoallergic Dermatitis from 8-Methoxypsoralen

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Summary. A 36 year old woman with psoriasis vulgaris developed generalized photoallergic dermatitis to 8-methoxypsoralen after 16 uneventful treatments with 8-methoxypsoralen und UVA (PUVA). The diagnosis of photoallergy was confirmed by re-exposure to oral 8-methoxypsoralen and total body UVA irradiation; phototests using topical and oral 8-methoxypsoralen with a high intensity monochromator or with a new high intensity light apparatus for the delivery of UVA; and histological studies. Photoallergy occurred only with UVA, but not with UVB or UVC. There was no photoallergy following trimethylpsoralen.

Key words: Photoallergic Dermatitis – 8-methoxypsoralen – UVA – PUVA

Zusammenfassung. Eine 36jährige Patientin mit Psoriasis vulgaris entwickelte nach 16 8-Methoxypsoralen-UVA-(PUVA)-Behandlungen eine generalisierte photoallergische Dermatitis auf 8-Methoxypsoralen. Die Photoallergie konnte sowohl nach lokaler als auch nach oraler 8-Methoxypsoralen-Applikation und UVA-Ganzkörperbestrahlungen oder Lichttestungen mit Hilfe eines Hochintensitätsgittermonochromators oder eines neuen Lichtleitergerätes ausgelöst werden. Histologische Untersuchungen bestätigten die Diagnose. Die Photoallergie trat nur nach UVA-, jedoch nicht nach UVB- oder UVC-Bestrahlung auf. Auf Trimethylpsoralen kam es nicht zu einer photoallergischen Dermatitis.

Schlüsselwörter: Photoallergische Dermatitis – 8-Methoxypsoralen – UVA – PUVA

Photochemotherapy with orally administered 8-methoxypsoralen (8-MOP) and long wave ultraviolet light (UVA), i.e. PUVA-therapy, is used in many dermatological centers. Very good results, especially in severe psoriasis, have been reported by several investigators [9–11,17,20,21].

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PUVA-therapy is associated with a variety of well known side-effects. The most frequent of these are pruritus in 8% [11] to 15% [21]; nausea in 5% [21] to 8% [11]; and localized severe erythema or even blistering in 4–20% [21] or 23% [20]. Recently other uncommon side-effects such as subungual hemorrhage, hypertrichosis, nevus spilus-like hyperpigmentation, and acneiform eruptions were observed [13]. Photoallergy after topically applied 8-MOP [7, 19], and to 8-MOP, 5-MOP and IMP [14] were recently reported. Photoallergic dermatitis induced by PUVA, not heretofore reported, was observed by us and is the subject of this report.

Photoallergy is defined as an „acquired altered photoreactivity dependent on an antigen-antibody or cell-mediated hypersensitivity state" [4]. Less time and less energy are required to evoke photoallergic reactions compared to phototoxicity. Histologically photoallergy looks very much like contact allergy with superficial and deep inflammatory lymphocytic infiltrates, edema, spongiosis, and negligeable alterations on the keratinocytes [4, 7].

Report of a Case

A 36 year old female patient with wide-spread chronic psoriasis vulgaris for 22 years began PUVA-therapy on October 1, 1976. The patient, who weighed 56 kg, was treated with 40 mg of 8-MOP tablets (Meladinine®, Basotherm, Germany) 2 h prior to UVA irradiation in a high intensity stand-up box. This box is equipped with 60 Philips TL 40W/09 and 60 Philips TL 20W/09 fluorescent lamps (Benke, Germany). The intensity at the center of the box is 8.0 mW/cm^2. The initial dose was 2.0 J/cm^2. Treatment was performed four times weekly. After 16 treatments over a period of 4 weeks, the patient was cleared to 95% of her psoriasis. At this time she received 40 mg of 8-MOP and a UVA-dose of 10.0 J/cm^2 on November 2, 1976. Eight hours later the patient developed a generalized itchy dermatitis.

Dermatological Findings. On November 3, 1976, 18 h after her last PUVA-treatment, almost the entire body of the patient was covered by a diffus erythema, visible despite hyperpigmentation. In addition, there were myriad, discrete tiny papules. The body areas which had received the highest light intensity, namely the anterior and posterior trunk, lateral upper arms and anterior thighs, were most severely involved (Fig. 2A). The clinical diagnosis was allergic dermatitis. Polymorphic light eruption was excluded because of the wide-spread clinical manifestation.

Investigative Procedures; Light Sources

High Intensity Stand-up Box. Equipment and output are described above.

High Intensity Grating Monochromator. This monochromator (Bausch & Lomb, U.S.A.) is equipped with a super pressure mercury lamp (HBO 200, Osram, Germany). A band-width of 19.2 nm centered at 370 nm was chosen (Fig. 1A). The intensity under these conditions was 5.6 mW/cm^2.

New High Intensity Apparatus with Flexible Light Guide. This instrument is also equipped with a super pressure mercury lamp (HBO 200, Osram, Germany). The UVA irradiation is conducted by a liquid filled core. A removable filter (WG 345, Schott, Germany) at the exit surface of the light guide transmits UVA irradiation (320–400 nm) and absorbs UVB and UVC irradiation ($<$ 320 nm) (Fig. 1B). Total output under these conditions is 2040 mW/cm^2. Details of this apparatus are reported elsewhere [16, 18].

Dosimetry

The output of the high intensity stand-up box was measured with a UVA-meter (Black-Ray Ultraviolet Meter, model J-221, Ultraviolet Products, U.S.A.), and a PUVA-Meter (Waldmann, Germany). The output of the high intensity monochromator and the new light apparatus with the flexible light guide was measured with a thermopile, model 17 and a watt meter, indicator model 154 (Laser Instrumentation Ltd, England).

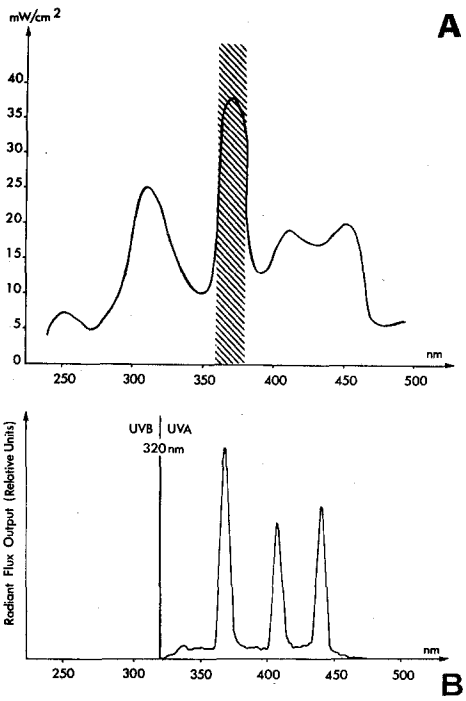

Fig. 1A and B
Spectral characteristics of light sources.
A Wave -length and output of the monochromator. The shaded bar indicates the wave-length used. **B** Wave-length distributions in relative units of the new light apparatus. There is no UVB. High peak around 366 nm

Drugs

Oral 8-MOP was available as 10 mg tablets (Meladinine®, Basotherm, Germany) and 10 mg capsules (Oxsoralen®, Elder, U.S.A.). The contents of the tablets was kindley disclosed by the manufacturer (written communication Dr. Saueressig, Basotherm, Biberach an der Riß, Germany, December 30, 1976) as follows: one tablet contains 9-methoxy-7H-furo [3.2 g] [1] benzopyrane-7-on 10.0 mg, lactose, corn starch, gelatine, magnesium stearate 0.5 mg.

Trimethylpsoralen (TMP) was available as 5 mg sugar coated pills (Trisoralen®, Elder, U.S.A.). One pill contains 4,5',8-trimethylpsoralen 5 mg, lactose 150 mg, talcum 6 mg, magnesium stearate 1 mg, and sugar 88 mg. Topical 8-MOP was available as a 0.15 % solution in 70 % isopropyl alcohol (Meladinine®, Basotherm, Germany).

Magnesium Stearate. This was kindly supplied by the manufacturer.

Testing Procedure. The testing procedure is summarized in Table 1.

Wave Length Dependency of Photoallergy

Four different wave lengths were selected to determine the wave length dependency of the photoallergic reaction. One hour prior to this, 0.15 % 8-MOP solution was applied to the skin.

UVC = 250 ± 10 nm, 0.180 J/cm^2 ≙ 11/2 MED,
UVB = 290 ± 10 nm, 0.150 J/cm^2 ≙ 2 MED,
UVB/UVA = 320 ± 10 nm, 0.150 J/cm^2 ≙ 2 MED,
UVA = 370 ± 19.2 nm, 5.0 J/cm^2.
Readings after 6 and 24 h.

Further 40 mg 8-MOP were given orally 2 h before application of 2.5 J/cm^2 (stand-up box, total body irradiation).

Test sites were the right and left flanks and inner sides of the upper arms. Readings were done immediately, after 16, 24 and 48 h. For comparison the exposure times for isodoses are given as follows:

stand-up box	10.0 J/cm^2 ≙ 21 min
monochromator	10.0 J/cm^2 ≙ 30 min
new light apparatus	10.0 J/cm^2 ≙ 41 s

Table 1. Photoallergic dermatitis from 8-MOP. Testing procedure and results

Drug	UVA-Dose (J/cm^2)	Time Interval	Reaction
	Stand-up box UVA > 320 nm		
Oral			
1. ∅	10.0		–
2. 40 mg 8-MOP t	∅		–
3. 40 mg 8-MOP t	7.8	2	+
4. 40 mg 8-MOP t	8.6	2	+
5. 40 mg 8-MOP t[d]	10.0	2	+
6. 40 mg 8-MOP c	6.5	2	+
7. 40 mg TMP p	10.0	2	–
8. 2 mg magnesium stearate[a]	10.0	2	–
9. 2 mg magnesium stearate[a]	∅		–
	Monochromator 370 ± 19.2 nm		
Oral			
1. 40 mg 8-MOP t	2.0	2	–
40 mg 8-MOP t	5.0	2	–
40 mg 8-MOP t	10.0	2	–
40 mg 8-MOP t	12.0	2	–
40 mg 8-MOP t	16.8	2	+
2. 40 mg 8-MOP c[b]	16.8	2	+
Topical			
3. 0.15% 8-MOP s	1.0	1	+
0.15% 8-MOP s	3.0	1	+
0.15% 8-MOP s	10.0	1	+
4. 0.15% 8-MOP s	2.0	24	–
0.15% 8-MOP s	5.0	24	–
0.15% 8-MOP s	10.0	24	–
5. ∅	2.0		–
	5.0		–
	10.0		–
6. 0.15% 8-MOP s	∅		–
	New Light Apparatus UVA > 345 nm		
Oral			
1. 40 mg 8-MOP t	10.0	2	–
40 mg 8-MOP t	20.0	2	–
40 mg 8-MOP t	30.0	2	+
40 mg 8-MOP t	40.0	2	+
2. 40 mg 8-MOP c	10.0	2	–
40 mg 8-MOP c	20.0	2	–
40 mg 8-MOP c	30.0	2	+
40 mg 8-MOP c	40.0	2	+
3. 40 mg TMP p	10.0	2	–
40 mg TMP p	20.0	2	–
40 mg TMP p	30.0	2	–
40 mg TMP p	40.0	2	–
Topical			
4. 0.15% 8-MOP s	1.0	1	+
0.15% 8-MOP s	3.0	1	+
0.15% 8-MOP s	5.0	1	+
0.15% 8-MOP s	10.0	1	+

Table 1. (Continuation)

Drug	UVA-Dose (J/cm^2)	Time Interval	Reaction
	New Light Apparatus UVA > 345 nm		
5. Ø	1.0		–
	3.0		–
	5.0		–
	10.0		–
6. 0.15% 8-MOP s	Ø		–

t = tablets; c = capsules; s = solution; p = sugar coated pills; [a] = equivalent of 40 mg tablets; [b] = only the powdered contents; Ø = not given; [d] = last PUVA treatment

Histology

Two biopsies were obtained, one 18 h after PUVA-treatment (4 h after clinical outbreak of the photoallergic dermatitis); and one 18 h after the monochromator testing with 16.8 J/cm^2 (4 h after clinical appearance of the photoallergic dermatitis in the test-site).

Results

Photoallergic dermatitis to 8-MOP in this patient could be elicited repeatedly under various experimental procedures. It was not possible to induce an abnormal reaction to TMP (Table 1).

Oral 8-MOP

The patient was re-exposed twice to standard doses of 8-MOP and UVA in the stand-up box and developed within several hours wide-spread papulo-vesicles (Fig. 2A). The intensity of the eruption increased over the next 10 h and resolved without sequelae. There was no Koebner phenomenon, and the patient remained almost free from psoriatic lesions for the next 7 months. Furthermore we were able to induce a photoallergic dermatitis in loco with either the monochromator or the new light apparatus.

With the *oral route* and the *monochromator*, more than 12 J/cm^2 were necessary for a positive reaction (Table 1).

With the *oral route* and the *new light apparatus*, lesions of photoallergic dermatitis were reproduceable with 30.0 and 40.0 J/cm^2, but not with less UVA (Table 1).

Topical 8-MOP

Positive reactions were obtained within 16–20 h, either with the monochromator (Fig. 2B) or the new ligth apparatus, with UVA doses between 1.0 and 10.0 J/cm^2 (Table 1). With increasing doses of UVA the reaction increased from a mere papulo-vesicular dermatitis to severe erythema, edema and bulla formation. The severe test reactions following the highest UVA doses were almost indistinguishable from a phototoxic dermatitis, except for the short time interval between exposure

Fig. 2A and B. Photoallergic dermatitis to 8-MOP and UVA. **A** Papulo-vesicular lesions on the flank 18 h after PUVA-therapy (stand-up box) and 4 h after onset of clinical lesions

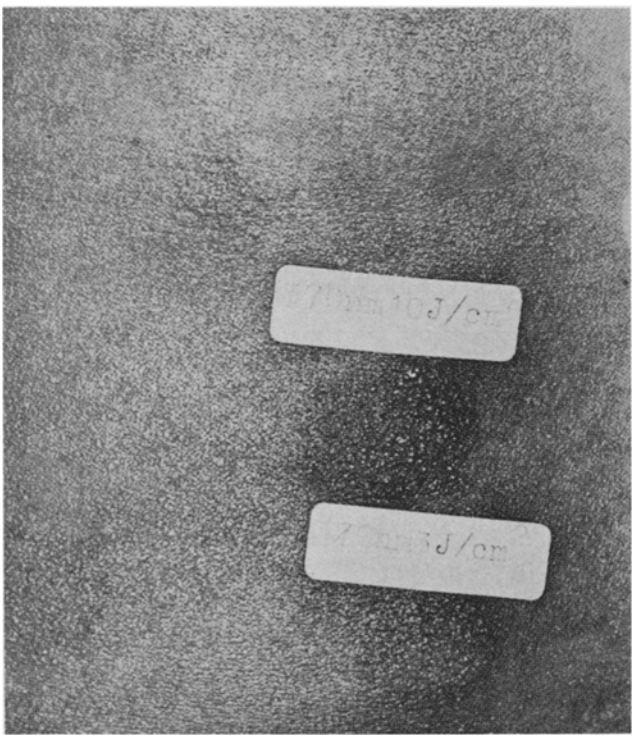

Fig. 2B
Reproduction of photoallergic dermatitis. Papulo-vesicular lesions on the flank 24 h after testing procedure (8-MOP topically, monochromator)

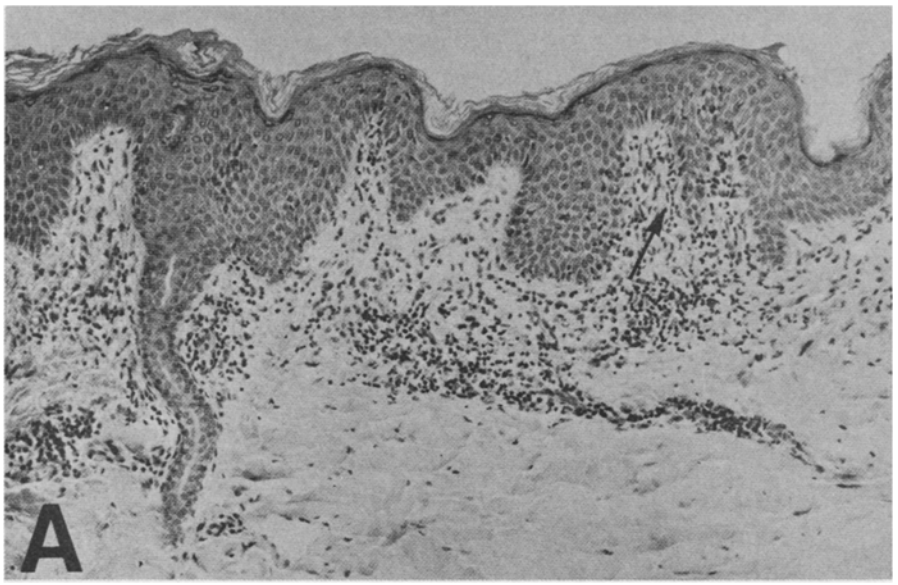

Fig. 3 A and B. Photoallergic dermatitis to 8-MOP and UVA. **A** Photoallergic dermatitis from lesion in Figure 2A. Lymphocytic infiltrate in the upper dermis and centered around an acrosyringium. Initial spongiosis (↑). H.-E. × 500

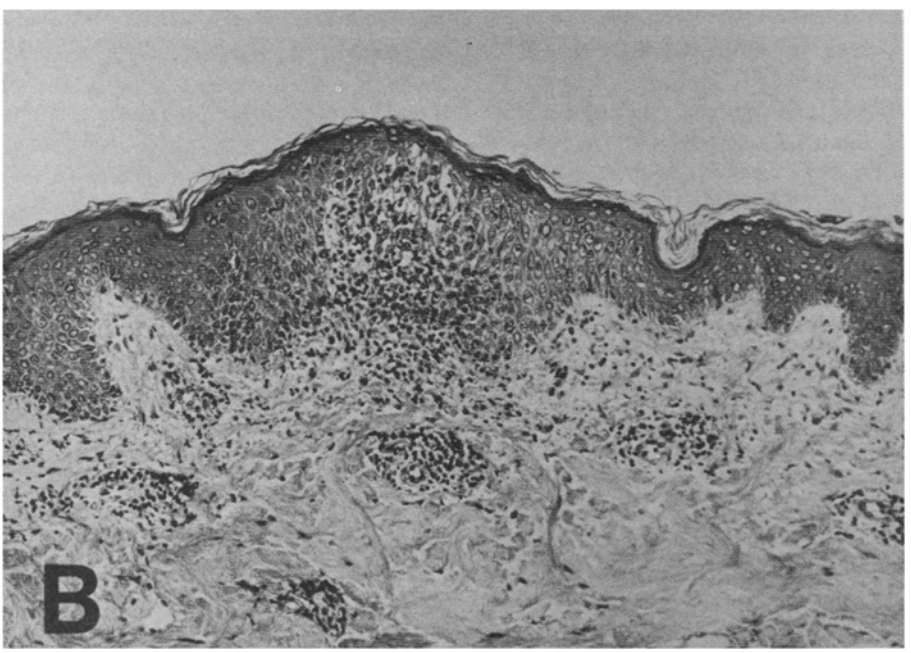

Fig. 3 B. Photoallergic dermatitis from lesion in Figure 2B. Spongiosis and perivascular round cell infiltrate in the upper dermis. H.-E. × 500

and onset. In contrast, when the time between 8-MOP application and UVA irradiation was extended from the usual 1 h period to 24 h, negative results were obtained with 2.0 – 10.0 J/cm^2 with the monochromator (Table 1). Controls with either UVA alone, 8-MOP alone, or magnesium stearate alone were negativ.

Wave Length Dependency of Photoallergy

Photoallergic dermatitis could be elicited only with UVA (370 nm), but not with UVB (290 nm), UVB/UVA (320 nm), nor with UVC (250 nm). After oral application and total body irradiation in the stand-up box 2.5 J/cm^2 were sufficient to induce a dense, pruritic, papulo-vesicular dermatitis.

Histology

The biopsy from the photoallergic dermatitis (17th PUVA-treatment) revealed a dense, predominantly lymphocytic infiltrate around blood vessels in the upper part of the dermis. The inflammatory cell infiltrate was also present around sweat ducts and acrosyringia (Fig. 3A). There were several foci of slight to moderate spongiosis.

The biopsy from experimentally induced photoallergic dermatitis showed also typical features of photoallergic dermatitis: superficial and deep perivascular round cell infiltrate, several foci of spongiosis, and absence of sunburn cells (Fig. 3B).

Discussion

The differential diagnosis to be considered in this patient includes phototoxicity, photoallergy and polymorphous light eruption.

Phototoxicity is defined as „a light-induced injury of the skin, which is independent of allergic mechanisms. These reactions may occur in everybody if enough light energy and, in the case of a photosensitized response, enough of the photosensitizer is present" [4].

Histologically the degeneration of epidermal cells is striking, especially if the photosensitizing agent is applied to the skin. Dyskeratotic cells, cell edema, and so-called sunburn cells are found. If the photoactive chemical is taken systemically, epidermal changes may be minimal. There are only a few inflammatory cells in the upper dermis [4]. Histological features of phototoxicity to topically [22] or orally [1, 22] applied 8-MOP are described in detail.

The definition of *photoallergy* is given in the introductory paragraph. Clinically photoallergic reactions have a crescendo character, wide-spread distribution with flares, and are associated with pruritus. Morphologically photoallergy includes densely set innumerable papulo-vesicles. Two types of photoallergy are recognized: photocontact allergy and photoallergy after oral or parenteral application of the allergen. Photocontact allergy to 8-MOP has been described earlier [7,14,19], but not photoallergy following oral intake of this drug. Histologically the key feature is a predominantly perivascular round cell infiltrate in the upper and middle dermis.

These cells then move to the epidermis and cause spongiosis. The extent of spongiosis depends on the time of the biopsy. Conversely epidermal cell damage is slight with hardly any sunburn cells.

Polymorphous light eruptions are defined as „abnormal reactions to solar energy characterized by eczematous, papular, and plaque-like lesions which appear several hours to several days after sun exposure" [5[. Lesions are mainly confined to sun-exposed areas with no tendency to flares. Histologically polymorphous light eruptions have a polymorphic picture depending on the type of the clinical lesion. Patchy perivascular infiltrates of lymphocytic cells in the middle and deeper dermis are characteristic. Dilated blood vessels and edema are common; spongiosis is associated with the eczematous type [2, 5]. Histological differential diagnosis are early lesions of lupus erythematosus, Jessners lymphocytic infiltration and other types of lymphomas.

Diagnostic procedures in the aforementioned conditions include: patch tests, photopatch tests (with either topical or oral drug application), light testing with various wavelengths. In vitro techniques are available for certain types of allergies (lymphocyte migration, lymphocyte stimulation, etc.).

Although psoralens have been used for decades for the treatment of vitiligo [3], for several years in the treatment of psoriasis [10,11,17,20,21] and recently for other dermatoses [8,12,15], photoallergic dermatitis has not been reported to be associated with their oral use. We were able to reproduce repeatedly the photoallergic dermatitis in this patient either after re-exposure under PUVA-like conditions or with experimental procedure in loco. *In loco* higher doses of UVA after oral 8-MOP application were necessary to reproduce the photoallergic dermatitis with the monochromator or the new light apparatus than with the total body UVA irradiation in the stand-up box. For the latter 6.5 J/cm^2 were sufficient, compared to 16.8 J/cm^2 with the monochromator. We have no explanation for this phenomenon. With the *topical route* of 8-MOP application 1.0 J/cm^2 induced allergic dermatitis (Table 1). Interestingly, the UVA doses necessary for the reproduction of the papulo-vesicular dermatitis in the stand-up box decreased with repeated challenges to 8-MOP. Initially 10.0 J/cm^2 had to be given, but later only 8.6, 7.8, and finally 6.5 J/cm^2 were sufficient.

The fact, that more UVA was needed for positive reactions with the new light apparatus (30.0 – 40.0 J/cm^2) than with the monochromator (16.8 J/cm^2) is explained by the spectral distribution of these two light sources (Fig. 1). The output of the monochromatic light is centered around 370 $\pm$ 19.2 nm, which is thought to be the peak of the action spectrum of 8-MOP. The spectral range of the new light apparatus is much broader (Fig. 1B), and therefore only parts of the measured dose were actually contributing to the action spectrum.

The photoallergic reaction could be separated from the well known phototoxic properties of this compound. The following criteria support the diagnosis of photoallergy in this patient. a) The short time interval to onset and peak of reaction less than 24 h (phototoxic reactions to 8-MOP take 24 – 28 h for their development with a climax at 72 h); b) clinical appearance of wide-spread lesions with tiny dense papulo-vesicles; c) histological findings of a lymphocytic infiltrate in the upper dermis coupled with spongiosis and lack of necrotic keratinocytes (so-called sunburn cells). With very high doses of UVA blistering occurred and at that point photoallergic and phototoxic reactions were present at the same time.

Undue reactions from additives to this photoallergic reaction had to be excluded. The tablets, but not the solution, contain lactose, corn starch, gelatine,

and magnesium stearate. Of these, only the latter chemical is able rarely to induce an allergic dermatitis [6]. Photoallergic reactions to this salt are not known. Our own control experiments were negative.

The occurrence of photoallergic dermatitis necessitated the termination of PUVA-therapy with 8-MOP in our patient. Retesting after one year under similar conditions disclosed an unaltered reactivity of the patient with typical features of photoallergy. Instead of 8-MOP, TMP may be used for maintenance therapy. Tests with 5-MOP are pending; this chemical is not available to us at the present time. This rare side-effect should not detract from the therapeutic effectiveness of the PUVA-therapy.

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