PUVA keratosis: a clinical and histopathological entity associated with an increased risk of non-melanoma skin cancer

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A clinical and histopathologic entity associated with an increased risk of nonmelanoma skin cancer

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Background: Various types of hyperkeratotic lesions can be observed in patients with psoriasis treated with PUVA. Clinically it can be difficult to classify them and to differentiate benign from malignant hyperkeratotic lesions. Recently, we introduced the term *PUVA keratosis*, which we regard as a distinct entity.
Objective: The purpose of the study was to describe in more detail the clinical and histopathologic features of PUVA keratoses and to investigate a possible relation with nonmelanoma skin cancer.
Methods: A group of 13 psoriasis patients with PUVA keratoses was studied and compared with 247 psoriasis patients without these keratoses, who had also received long-term therapy with PUVA.
Results: The presence of PUVA keratoses was associated with an increased risk of nonmelanoma skin cancer. The estimated relative risk for skin cancer in patients with PUVA keratoses, adjusted for age, sex, and UVA dose, as compared with psoriasis patients without these keratoses, who had also received long-term PUVA treatment, was 6.5 (95% confidence interval, 1.3 to 32.1). Squamous cell carcinomas contributed the most to this increased risk.
Conclusion: PUVA keratoses are associated with an increased risk of nonmelanoma skin cancer. Therefore careful clinical follow-up of psoriasis patients with PUVA keratoses is necessary, and cessation of PUVA treatment should be considered.
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Various types of benign hyperkeratotic lesions can be observed in patients with psoriasis.[1-4] Recently, we described PUVA keratosis in a long-term follow-up study of 260 patients with psoriasis, who were treated with 8-methoxypsoralen and UVA radiation (PUVA) between 1975 and 1988.[5] This keratosis has been recognized for years by PUVA investigators, but a thorough study has not been done. A PUVA keratosis was defined as a raised papule with a broad base and a diameter of several millimeters to about 1 cm. The top of the lesion is hyperkeratotic and scaly and has a warty appearance (Figs. 1 and 2).

In the present study, we describe in more detail the clinical and histopathologic features of PUVA keratosis. In addition, the prevalence of nonmelanoma skin cancer in patients with PUVA keratoses was compared with the prevalence of nonmelanoma skin cancer in a large group of PUVA-treated psoriasis patients without these keratoses and the relative risk for development of nonmelanoma skin cancer was assessed in the patient group with PUVA keratoses.

PATIENTS AND METHODS

Between 1975 and 1988, 334 patients with psoriasis were treated with oral photochemotherapy (PUVA) in

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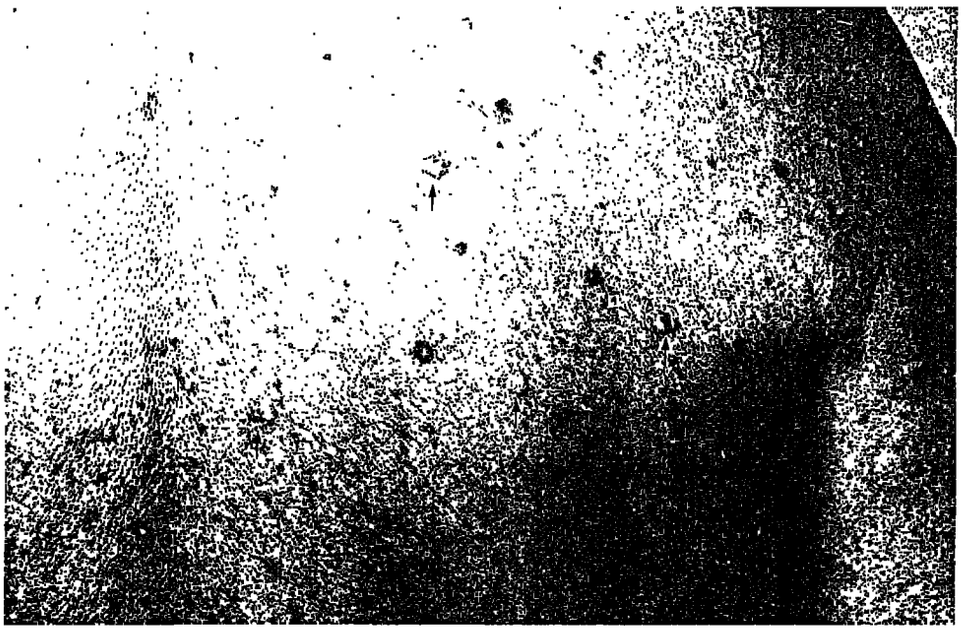

Fig. 1. Four typical PUVA keratoses *(arrows)* and numerous PUVA freckles are present on the back.

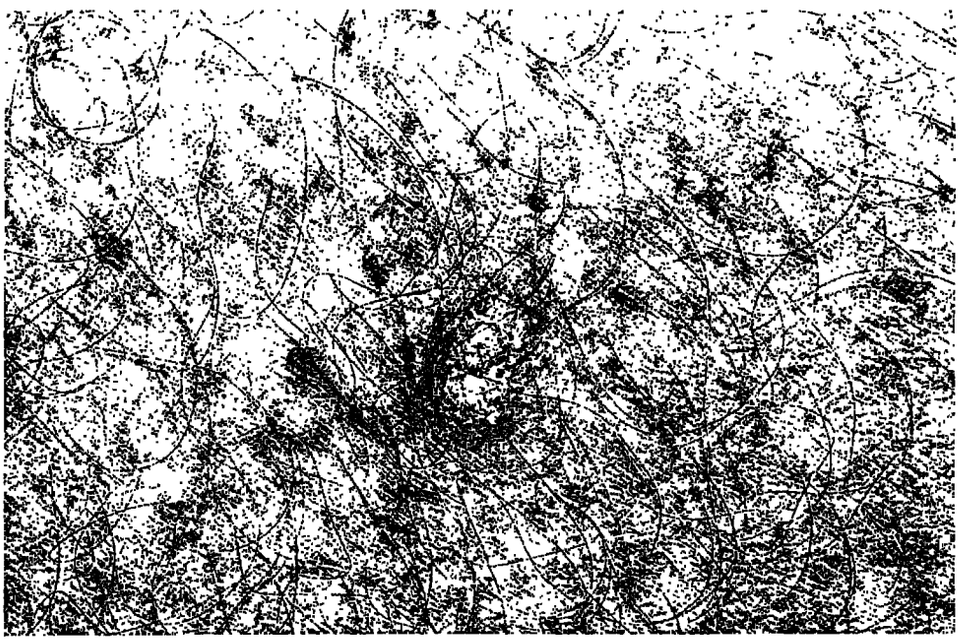

Fig. 2. Detail of PUVA keratosis.

the Leiden University Hospital. Seventy-four patients did not participate in the follow-up study for reasons mentioned in our previous article.[5] Therefore a total of 260 patients were examined in 1987. Before 1987, the presence of benign skin tumors was not documented. Of these 260 patients, 13 patients with PUVA keratoses were selected for further characterization.

All patients had been treated with a standard PUVA regimen. 8-Methoxypsoralen (0.5 to 0.6 mg/kg of body weight) was taken orally 2 hours before treatment. The initial UVA dose of each patient depended on skin sensitivity to UVA[6] and ranged from 0.3 to 1.0 joule/cm^2. The clearing treatment consisted of a three-times-a-week schedule, in which the dose was elevated by 10%, 20%, or

Table I. Baseline characteristics of the patients with and without PUVA keratoses

	Patients with PUVA keratoses	Patients without PUVA keratoses	Differences between the groups (95 % CI)
No. of patients	13	247	
Male/female ratio	12:1	154:93	
Skin type			
II	2	14	
III	10	203	
IV	1	21	
V	—	9	
Duration of follow-up (yr) (mean ± SD)	10.6 ± 1.7	8.6 ± 2.8	2.0 (0.45;3.6)
Age at the start of PUVA (yr) (mean ± SD)	52.7 ± 12.6	42.5 ± 4.6	10.2 (2.1;18.3)
Age at physical examination (yr) (mean ± SD)	63.9 ± 11.4	51.4 ± 14.4	12.4 (4.4;20.4)
No. of treatments (mean ± SD)	179 ± 59	98 ± 58	81.0 (48.5;114.0)
Dose of UVA (J/cm^2) (mean ± SD)	1693 ± 801	776 ± 713	917 (516;1319)
No. of patients with NMSC (%)	4 (30.8)	7 (2.8)	
Total No. of NMSC	10	27	
No. of SCCs	7	6	
No. of BCCs	3	21	

BCC, Basal cell carcinoma; *CI*, confidence interval; *NMSC*, nonmelanoma skin cancer; *SCC*, squamous cell carcinoma; *SD*, standard deviation.

30% every other session. Immediately after clearing, a maintenance regimen was followed, during which the frequency was gradually reduced to one treatment every 2 or 3 weeks. The last administered UVA dose was kept unaltered, ranging from 2 to 15 joules/cm^2. If the psoriasis relapsed, the treatment frequency was temporarily increased.

The patients with and without PUVA keratoses were compared as to age, sex, skin type, previous use of arsenicals, methotrexate, or etretinate, exposure to x-rays or UVB, total UVA dosage, and the occurrence of nonmelanoma skin cancer. Skin types were defined according to Johnson and Lookingbill.[7] It was determined whether PUVA keratoses were localized in sun-exposed areas.

Skin biopsies of representative lesions were performed in 10 patients. Routinely stained (hematoxylin and eosin; Verhoeff-van Gieson) sections of PUVA keratoses were examined. The presence of orthokeratosis, parakeratosis, acanthosis, papillomatosis, apoptosis, atypical epidermal cells, inflammatory infiltrate, and elastosis was recorded.

To compare the prevalence of nonmelanoma skin cancer in the group of psoriasis patients with PUVA keratoses and the group without these keratoses, the chi-square test was applied. Values of p less than 0.05 were considered to indicate statistical significance. Differences between the groups in mean age, mean number of treatments, and mean UVA dose were calculated by the unpaired two-tailed Student t test. Results were expressed as means ± standard deviation.

The crude and the adjusted odds ratios with 95% confidence interval were calculated for estimation of the relative risk of nonmelanoma skin cancer for psoriasis patients with PUVA keratoses, compared with patients without these keratoses. This was done by maximum likelihood estimation in a logistic model (Egret, Statistics and Epidemiology Research Corporation, Seattle, Wash.). The crude odds ratio was adjusted for the UVA dose and age and sex of the patient. The same method was applied to assess the relative risk of PUVA keratoses in relation to the UVA dose and age and sex of the patient.

For statistical analysis the number of person-years at risk was computed by the Kaplan-Meier analysis. The number of person-years was calculated between arbitrarily chosen opening and closing dates. As the opening date for this calculation the date of the first PUVA treatment was used. As closing date we used the date of diagnosis of the first skin cancer or the end of the study on Dec. 31, 1987.

RESULTS

Clinical data

The mean age of all patients at the start of PUVA treatment was 43.4 years (range 20 to 86 years) and

Table II. Estimated relative risk (odds ratio) of PUVA keratoses in relation to the dose of UVA and age and sex of the patient

	Crude odds ratio (95% CI)	Adjusted odds ratio (95 % CI)*
UVA dose (J/cm^2)		
600-1199 vs 0-599	8.8 (0.90;211.8)	9.6 (1.0;91.3)
≥1200 vs 0-599	17.9 (2.2;391.1)	16.2 (1.9;137.0)
Age (yr)		
40-59 vs 20-39	1.4 (0.12;35.5)	1.0 (0.10;10.5)
≥60 vs 20-39	7.7 (0.94;166.3)	5.8 (0.67;49.7)
Sex		
Male vs female	7.1 (0.97;100.0)	5.8 (0.71;47.5)

CI, Confidence interval.
*Odds ratio with 95% CI, calculated with a logistic regression model, adjusted for the dose of UVA, age at physical examination, and sex of the patient.

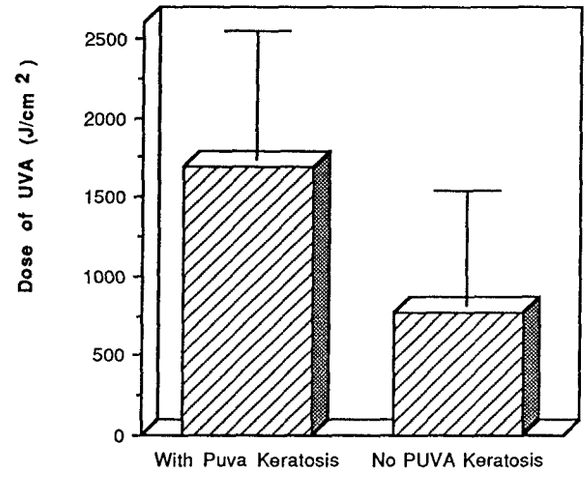

Fig. 3. Cumulative UVA dose in patients with and without PUVA keratoses (mean ± SD).

at physical examination 52.1 years (range 20 to 84 years). A total of 18 PUVA keratoses was observed in 13 patients. PUVA keratoses were predominantly observed in men (male/female ratio = 12:1). One patient had had a basal cell carcinoma (BCC), and one patient was treated earlier with methotrexate. None of the patients had used etretinate or had been treated with UVB or x-rays. The mean individual cumulative UVA dose of the patients in whom PUVA keratoses developed was 1693 ± 801 joules/cm^2. The mean period between the start of PUVA therapy and the diagnosis of PUVA keratosis was 9.1 ± 2.3 years. Two patients had skin type II, 10 patients had skin type III, and 1 patient had skin type IV. The localization of the PUVA keratoses on sun-exposed versus nonexposed areas of the skin was 7:11. They were primarily observed on the trunk and thighs. The PUVA keratoses were in general detected later than the cutaneous malignancies. Most PUVA keratoses were recorded for the first time in 1987, when the PUVA-treated patients were screened systematically for benign skin tumors.

In Table I a comparison is made between the group with PUVA keratoses and the group without these keratoses. The mean cumulative dose of UVA in the group with PUVA keratoses was significantly higher than that in the group without PUVA keratoses (Fig. 3). The mean difference with 95% confidence interval was 917 joules/cm^2 (516 to 1319 joules/cm^2). The difference between the mean ages at the start of PUVA treatment of the two groups was also statistically significant: 10.2 years (2.1 to 18.3 years). The crude odds ratios for the development of PUVA keratoses and the odds ratios adjusted for the UVA dose and age and sex of the patient are depicted in Table II.

Until the closing date of our study,[5] in 4 of the 13 patients with PUVA keratoses a total of 10 malignant skin tumors (7 squamous cell carcinomas [SCCs] and 3 BCCs were found. In 75% of cases, the SCCs were graded as highly differentiated. Six SCCs and one BCC were localized on non-sun-exposed areas of the skin. In 7 of the 247 PUVA-treated psoriasis patients without PUVA keratoses, 27 skin carcinomas were diagnosed (6 SCCs and 21 BCCs). The difference between the two groups is highly significant ($p < 0.0001$). The crude odds ratio with 95% confidence interval to develop nonmelanoma skin cancer in the psoriasis patient group with PUVA keratoses, compared with the group without these keratoses, was 15.2 (3.8 to 61.6). Adjustment of this odds ratio for the UVA dose and age and sex of the patient resulted in an estimated relative risk of 6.5 (1.3 to 32.1).

Five years after the start of PUVA treatment the cumulative incidence of skin cancer in the patients with PUVA keratoses was 15% (95% confidence interval, 4% to 49%) and in the patients without PUVA keratoses 2% (95% confidence interval, 1% to 5%). Eight years after the start of PUVA treatment the incidence of skin cancer in the PUVA keratoses group had increased to 31% (95% confidence interval, 13% to 63%) and to 4% (95% confidence interval, 2% to 7%) in the group without PUVA keratoses.

Table III. Histopathologic features of PUVA keratosis in 10 patients

Histopathologic features	Patient No.									
	1	2	3	4	5	6	7	8	9	10
Hyperkeratosis	++	+	+	++	++	−	+	++	+	++
Parakeratosis	+	+	+	++	++	+	±	++	+	++
Acanthosis	+	+	++	++	++	+	+	++	+	+
Acantholysis	−	−	−	−	−	−	−	+	−	−
Papillomatosis	+	−	−	++	++	−	−	+	−	−
Apoptosis	−	+	−	−	−	+	−	+	++	+
Atypia	+	±	±	±	+	++	±	±	+	+
Mitosis	+	+	+	+	+	±	+	++	+	±
Infiltrate	±	+	+	+	+	+	+	+	++	+
Lymphocytic infiltration of basal layers of the epidermis	−	±	−	−	−	±	−	±	+	±
Elastosis	−	−	−	−	−	−	−	++	−	−

−, Absent; ±, slight; +, moderate; ++, prominent.

Histopathologic features

The frequencies of the observed histopathologic features of the PUVA keratoses are summarized in Table III. The punch biopsy specimens revealed an epidermis with a variable degree of acanthosis, orthokeratosis, focal parakeratosis, and some apoptotic cells. In half of the specimens, papillomatosis was observed. One lesion showed focal acantholysis. In the papillary dermis a mild perivascular, predominantly lymphocytic infiltrate, slightly invading the epidermis, was seen in half the specimens. Only mild atypia of keratinocytes was found in 50% of the cases, represented by minor variations in size and shape of cells and by minimal hyperplasia and hyperchromasia of the nuclei. Neither viral changes nor typical features of psoriasis were observed (Figs. 4 and 5). In only one PUVA keratosis on the cheek, was elastosis observed.

DISCUSSION

PUVA keratoses were localized on non-sun-exposed skin (i.e., the trunk and thighs) in 11 of 18 cases, suggesting a primary relationship between the development of these lesions and PUVA treatment.

In the clinical differential diagnosis psoriasis vulgaris, verruca vulgaris, hyperkeratotic papilloma, seborrheic keratosis, bowenoid or hypertrophic type of solar keratosis, lichenoid keratosis, tar keratosis, arsenical keratosis, and SCC should be considered. Neither arsenic nor x-radiation were etiologic agents in the development of PUVA keratoses because no patient had been exposed to them. Three patients had been treated with coal tar before they started PUVA therapy, suggesting that tar can be considered as a causal factor. Gotz[2] has described 92 cases of tar keratoses. However, none of our patients showed keratoses before initiation of PUVA therapy. In addition, tar keratoses have in general a distal location (90% hands and feet) in contrast with PUVA keratoses. PUVA keratoses differ from solar keratoses in that the latter appear in areas of actinic damage and are histopathologically characterized by more obvious atypia of epidermal cells and by marked elastosis. In all cases, the PUVA keratoses could be easily differentiated histopathologically from psoriasis vulgaris, viral warts, lichenoid keratoses, and SCCs.

Gupta et al.[4] described the development of discrete, gray-white, asymptomatic keratoses, approximately 4 mm in diameter, in 28 of 52 consecutive inpatients with psoriasis admitted for treatment with the modified Goeckerman regimen. Histopathologic examination of these keratoses differed from PUVA keratoses in that they usually showed orthokeratotic hyperkeratosis; parakeratosis was seen occasionally and papillomatosis was not observed. The dermis was essentially normal with a mild superficial perivascular lymphocytic infiltrate in some cases.

The number of patients with nonmelanoma skin cancer was significantly higher in the PUVA keratoses group, as compared with the number of skin carcinomas in the large group of psoriasis patients without these keratoses, who also had received long-term PUVA treatment. Five years after the start of the PUVA treatment 15% of the patients with PUVA keratoses had developed nonmelanoma skin cancer; after 8 years this number had increased to 31%. Only 4% of the patients without PUVA kera-

Fig. 4. PUVA keratosis. Acanthotic epidermis with parakeratosis and hyperparakeratosis and mild perivascular inflammatory infiltrate. (Hematoxylin-eosin stain; ×100.)

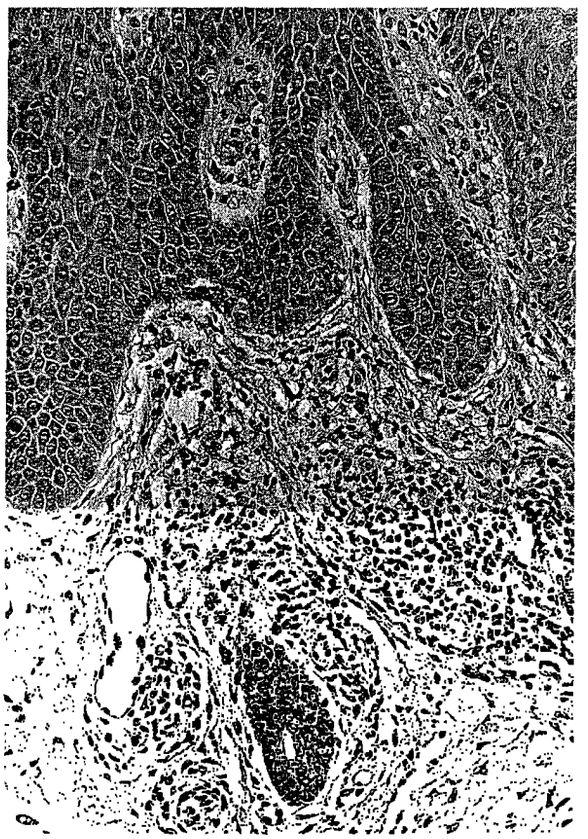

Fig. 5. Detail of PUVA keratosis: inflammatory infiltrate slightly invading epidermis. Apoptotic cells in spinous cell layer. (Hematoxylin-eosin stain; ×250.)

toses had developed skin cancer 8 years after the start of the PUVA treatment. Risk factors for the development of PUVA keratoses were aging, male sex, and the cumulative dose of UVA. The crude odds ratio of nonmelanoma skin cancer in the patient group with PUVA keratoses was 15.2 and the odds ratio adjusted for the UVA dose and age and sex of the patient was 6.5. It appeared that SCCs contributed most to the increased risk of skin cancer. It can be concluded that PUVA keratoses are associated with an increased risk of nonmelanoma skin cancer. Since we started a systematic screening for PUVA keratoses in 1987, most PUVA keratoses were detected later than the cutaneous malignancies. Therefore we have no conclusive evidence yet that PUVA keratoses are premalignant skin tumors. Such evidence can only be obtained by prospective studies in which PUVA-treated psoriasis patients are observed from the onset of this treatment. Because the premalignant nature of PUVA keratoses could not be excluded, they were removed by freezing with liquid nitrogen.

Because PUVA keratoses are associated with an increased risk of nonmelanoma skin cancer, careful clinical observation of psoriasis patients with PUVA keratoses is necessary and even cessation of the PUVA treatment should be considered.

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