Acta Dermatovener (Stockholm) 63: 215–221, 1983

LONG-TERM PHOTOCHEMOTHERAPY FOR PSORIASIS: A HISTOPATHOLOGICAL AND CLINICAL FOLLOW-UP STUDY WITH SPECIAL EMPHASIS ON TUMOUR INCIDENCE AND BEHAVIOR OF PIGMENTED LESIONS

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Abstract. A thorough clinical and microscopical investigation was conducted in patients with severe longstanding psoriasis maintained on long-term photochemotherapy with PUVA. 250 patients were reinvestigated after PUVA therapy for up to 7 years, 49% for 5 to 7 years. No serious side effects were observed. Occasional peculiar hyperkeratoses of a bowenoid type were seen in 3 patients (1.2%) and solitary lesions of actinic keratoses in 5 patients (2%). No occurrence of squamous cell carcinoma nor basal cell carcinoma was detected. Lentiginosis of varying degree was fairly common and seen in 33% and a very profuse disseminated lentiginosis in 4%. Six patients (2.4%) developed isolated, clinically dark and irregular lentiginous spots which on biopsy showed microscopically an aberrant morphology and were therefore classified as atypical lentigines. All of them had earlier been subjected to extensive courses of UVB treatment and 3 of them had history of earlier arsenic therapy. No malignant transformation was seen but those were for reasons of safety referred to the risk group category and may prove to be at particular risk on future PUVA therapy.

Key words: Photochemotherapy; PUVA; Follow-up study; Histopathological; Clinical; Tumour incidence

The efficacy of PUVA therapy for psoriasis is now well documented (1, 3, 7, 10, 11, 13, 15, 16). Long-term side effects have recently been discussed in some reports with observations including clinical and histopathological findings from several therapeutic centres (1, 2, 3, 4, 5, 6, 7, 10, 11, 13, 15, 16, 21). Special reports have been directed to possible influence on the melanocyte, pigmentation and nevocellular nevi, but also possible ophthalmological hazards (1, 3, 8, 9, 12, 14, 17, 20). The matter of greatest concern has been the possible induction of premalignant or malignant changes in patients on long-term therapy (3, 5, 6, 7, 10, 11, 13, 15, 16). An increased incidence of malignant neoplasm was reported in some studies but has not yet been seen in other investigations.

PUVA therapy has been given regularly in our department to patients for up to 7 years and our clinical impression has been that no convincing signs of malignancy have been observed. The purpose of the present study was to perform a thorough reinvestigation of all patients with severe longstanding psoriasis who have been subjected to repeated and more or less continous PUVA treatment. Besides clinical examination, several skin biopsies have been taken from both clinically normal-looking skin on exposed parts of the shoulder and gluteal regions and from lesions suspected of premalignant or malignant transformation. Special attention was devoted to any possible change in pre-existing nevocellular nevi and to the appearance of a varying degree of lentiginosis. Multiple biopsies from pigmented lesions were taken and processed for meticulous microscopical investigation.

MATERIAL AND METHODS

250 patients with severe longstanding psoriasis given PUVA therapy more or less continuosly for up to 7 years were investigated. The study included 93 women and 157 men. Clinical data such as mean age, duration of their disease prior to therapy, skin type, and earlier treatments with arsenic, methotrexate, or ionizing radiation are outlined in Table I. Most patients had also earlier received UVB treatment (91%) and many had travelled south for climate therapy of their psoriasis (61%). Other coexisting diseases in the patients are reported in Table II.

PUVA therapy was first introduced in 1974. An oral dose of approximately 0.6 mg per kg bodyweight was given 2 hours before the UVA irradiation. The initial UVA dose was about 1.5–2.5 $J \cdot cm^{-2}$ and was gradually increased by 0.25–1 $J \cdot cm^{-2}$ each time up to a maximum

Table I. *Clinical data of reinvestigated PUVA-treated patients (n=250)*

Females, No.	93 (37%)
Males, No.	157 (63%)
Mean age	47.3 years
Mean duration of psoriasis before treatment	22.4 years
Skin type I or II	25 (10%)
Skin type III or IV	225 (90%)
Earlier arsenic treatment	49 (20%)
Earlier methotrexate treatment	31 (12%)
Earlier ionizing radiation (grenz rays)	51 (20%)

Table III. *Data on PUVA treatment: total number of treatments and total UVA dose accumulated (no. of patients, 250)*

No. of treatments	No. of patients	Total UVA dose, $J \cdot cm^{-2}$	No. of patients
<20	31	<100	24
21–50	59	101–200	32
51–100	63	201–500	78
101–200	61	501–1 000	64
201>	36	1 001–2 000	35
		2 001>	17

dose of 20 $J \cdot cm^{-2}$, but many patients required considerably less before healing was achieved. UVA irradiation was provided by light sources giving longwave ultraviolet radiation ranging from 320 to 380 nm. intensity maximum around 365 nm. Lamp intensities were measured regularly with a Hewlett-Packard radiant flux meter or with a PUVA-meter (H. Waldmann Werk für Lichttechnik).

Initially, treatment was given 3 to 4 times per week during the period 1974 to 1977, but later 2 to 3 times per week. After total clearing, maintenance therapy was given once weekly for about 1–2 months afterwards for the majority of the patients. Because of the severity of their disease several patients have received repeated courses of PUVA treatment for several months 2–4 times annually or continuous regular treatment once or twice weekly.

During therapeutic irradiation, eye protection was provided by small black non-transparent glasses. The patients were furthermore instructed to wear Polaroid® sunglasses and to avoid sun exposure on the day of medication (19).

Therapeutic data with total number of treatments and total UVA dose accumulated given are reported in Table III. The time period from PUVA initiation until the follow-up investigation was 1–7 years; 49% were followed for 5 to 7 years (Table IV).

All patients were interviewed concerning noticeable side effects during PUVA treatment and a clinical examination was carried out with a thorough inspection of the whole body and with special attention paid to all skin lesions suspected of being malignant.

Punch biopsies were taken from clinically normal-looking skin on exposed areas of shoulder and gluteal regions in all patients except 3 who refused biopsy. Furthermore, all skin lesions suspected of being premalignant or malignant were biopsied and also all nevi clinically suspected to be junction or compound nevi.

A thorough ophthalmological study was also conducted in some of the patients, but the results are reported elsewhere (14).

Laboratory tests including sedimentation rate, hemoglobulin, leukocyte, red blood cell and thrombocyte count, serum creatinine and liver function tests with transaminases, were performed initially and later at 6–8 week intervals.

Table II. *Other coexisting diseases in PUVA-treated psoriatic patients (n=250)*

	No. of patients
Arthralgia	16
Atopic disease	20
Vitiligo	4
Diabetes mellitus	3
Hypothyreosis	1
Thrombocytopenia	1
Porphyria cutanea tarda	1
Crohn's disease	1
Pernicious anemia	1
Cataract	1

RESULTS

Clinical findings

The clinical data obtained from the 250 investigated PUVA-treated patients are given in Table I and data regarding other coexisting diseases in Table II. Total number of treatments and total cumulative UVA dose given are outlined in Table III. Duration from PUVA initiation to the follow-up investigation is seen in Table IV and 49% were followed for 5 to 7 years.

Among acute side effects observed during PUVA therapy (Table V), nausea (49%), pruritus (26%) and paresthesia (23%) predominated. Fatigue

Table IV. *Period from PUVA initiation to the follow-up investigation*

	Duration (years)						
	1	2	3	4	5	6	7
No. of patients (250)	14	31	36	47	78	40	4

Table V. *Acute side effects during PUVA therapy*

	No. of patients	%
Nausea	123	49
Pruritus	66	26
Paresthesia	58	23
Fatigue	53	21
Vertigo	50	20
Phototoxic reaction	45	18
Gastrointestinal disturbances	22	9
Headache	14	6
Leg oedema	5	2
Blisters	4	1.5

(21%) and vertigo (20%) was also fairly common. The paresthesia observed was frequently seen in the beginning but usually disappeared with further treatments. It was experienced as a burning or prickling sensation, but severe skin pain as reported elsewhere (18) was not seen. Infrequent reactions were leg oedema without any other sign of phototoxic reaction such as erythema or blistering. In 4 patients, blisters appeared on clinically normal-looking skin, usually on the legs and without any sign of preceding erythema.

The laboratory tests performed were normal but in 26 patients a slight rise in serum transaminases was noted and alcohol abuse seemed to be the relevant cause for most of them. After information and on further treatment, normalization occurred in all but 4 patients and then PUVA therapy was discontinued. No liver biopsies were performed.

Long-term side effects clinically observed are outlined in Table VI. A slight to moderate lentiginosis was fairly common and seen in 33% of the patients. A pronounced disseminated lentiginosis was noted in an additional 4%. Skin types I and II were twice as common among these patients as in the material as such. Hypertrichosis usually on face and extremities was observed in 4.5% of the patients. Pronounced actinic elastosis was seen in 2.5% of patients, whose ages ranged from 60 to 75 years. Furthermore, 2/6 (33%) had skin type II, which is an overrepresentation compared with 10% in the study group as such. Similarly, skin types I and II were found in 40% of those with actinic keratoses and an earlier course of arsenic treatment was twice as common among these patients as in the others, 40% vs. 20% (Table X).

Therapeutic data are shown in Tables VII, VIII and IX for those with profuse disseminated lentiginosis, pronounced actinic elastosis and actinic keratosis. The lentiginosis observed correlates well with the extensive therapy given. All of them had also earlier been subjected to UVB treatment. For those with pronounced actinic elastosis, age and earlier UVB treatment and solar exposure seemed to be the most relevant cause even though PUVA therapy might have been an additional promoting factor in some instances.

Histopathological findings

In all patients, biopsies were taken from clinically normal-looking skin on the shoulder and the gluteal region, but also from skin lesions which seemed abnormal. Skin biopsies were also taken from 5 healthy Caucasians with a mean age corresponding to that of the PUVA-treated patients. These controls all showed a completely normally configurated epidermis. A slight difference was observed between the epidermis from biopsies of the skin of the shoulder region and of the gluteal region, the latter showing slightly more pronounced rete ridges.

Biopsies from clinically normal-looking skin of PUVA-treated patients revealed an increased epidermal thickness in the shoulder region of 102 patients (41%) and in the gluteal region of 31 patients (13%). A significant epidermal melanosis was observed in 120 (49%) and 48 (19%) patients in shoulder and gluteal region respectively. Dermal melanosis was seen in 57 (23%) and 34 (14%) patients in biopsies from shoulder and gluteal regions.

Hyperkeratosis was repeatedly observed. This was mainly of the orthokeratotic type, sometimes of the retention type, but more often of proliferative with a concomitant epidermal hyperplasia with acanthosis. Parakeratosis or parahyperkeratosis was rarely observed and especially in connection with infraposed keratinocytic abnormalities. In 3 patients those epidermal cellular

Table VI. *Long-term side effects clinically observed in PUVA-treated patients*

	No. of patients	%
Lentiginosis	82	33
Lentiginosis, profuse	10	4
Hypertrichosis	11	4.5
Actinic elastosis (pronounced)	6	2.5
Actinic keratosis	5	2

Table VII. *Profuse disseminated lentiginosis in PUVA treated patients*

Patient	Age (yrs)	Skin type	No. of treatments	UVA-dose (cumulative $J \cdot cm^{-2}$)	Earlier arsenic therapy	Earlier Grenz rays	Earlier UVB therapy	Earlier MTX therapy
CB	32	II	278	1 337	−	−	+	−
LK	63	II	186	848	−	+	+	−
EA	60	III	237	1 770	+	+	+	−
SB	52	III	297	2 602	−	−	+	+
LJ	40	III	381	1 900	−	−	+	−
IM	31	III	470	2 052	−	+	+	−
AT	39	III	172	2 136	−	−	+	−
EW	70	III	192	1 287	+	−	+	+
EH	47	IV	224	840	−	−	+	−
ML	60	IV	172	1 276	−	−	+	+

aberrations were of bowenoid type, showing an evident poikilokaryonosis.

The clinically observed lentiginosis was documented histologically. However, 6 patients showed changes microscopically in biopsies from solitary very dark, clinically nevoid lesions, which were classified as atypical lentigo. This entity will be discussed later. Earlier treatment with arsenic was noted for 3 of them, methotrexate for 2 and all of them had earlier received significant amounts of UVB treatment. Solitary actinic keratosis was documented in 5 patients, 2 of them earlier treated with arsenic, and all but one with UVB therapy.

No squamous cell carcinoma nor basal cell carcinoma was observed among the investigated patients.

DISCUSSION

Numerous reports on the acute and long-term side effects of PUVA have now been published (1, 2, 3, 4, 5, 7, 8, 10, 11, 13, 15, 16) and also anecdotal reports of occasional cases of skin tumours believed to have been caused by PUVA treatment. The most commonly held theory is that PUVA has a tumour-promoting cocarcinogenic capacity which seems to be significant, especially in certain cases at risk such as in patients with fair, light-sensitive complexion belonging to skin types I or II and in those earlier treated with arsenic or ionizing therapy. Unfortunately, larger control populations of patients with psoriasis, of similar age distribution and as thoroughly monitored and investigated with biopsies as those given photochemotherapy are largely missing up to the present. However, this does not allow us to conclude that the suspected skin cancer promoting capacity of PUVA therapy is not a reality, but we should still follow up our patients continuously with careful monitoring. Nevertheless, some discrepancies do exist between the American (13, 15) and European (1, 3, 5, 7, 10, 16) PUVA studies concerning the skin cancer incidence which has not yet been shown to increase, according to several earlier European reports and the same was found in the present study of patients treated for up to 7 years. Almost half of our patients have now been followed up for up to 5 to 7 years. No squamous cell carcinoma or basal cell carcinoma has been found, but 3 patients

Table VIII. *Pronounced actinic elastosis in PUVA-treated patients*

Patient	Age (yrs)	Skin type	No. of treatments	UVA-dose (cumulative $J \cdot cm^{-2}$)	Earlier arsenic therapy	Earlier Grenz rays	Earlier UVB therapy	Earlier MTX therapy
SB	67	II	24	325	−	−	+	−
EJ	60	II	104	620	+	+	+	+
SF	72	III	16	45	+	−	+	−
HA	75	III	91	476	+	−	+	−
ÅV	61	IV	2	8	−	−	+	−
ES	72	IV	81	1 035	−	−	+	−

Table IX. *Actinic keratosis, Bowenoid changes and atypical lentigines in PUVA-treated patients*

Patient	Age (yrs)	Skin type	No. of treatments	UVA-dose (cumulative $J \cdot cm^{-2}$)	Earlier arsenic therapy	Earlier Grenz rays	Earlier UVB therapy	Earlier MTX therapy
I. *Actinic keratosis*								
VÖ	73	I	31	129	+	+	+	−
NS	77	II	32	102	−	−	−	−
BD	51	III	145	982	−	+	+	+
GG	74	III	286	1 384	+	+	+	−
ES	72	IV	81	1 035	−	−	+	−
II. *Bowenoid lesions*								
HL	62	III	18	22	−	−	+	−
BL	40	IV	292	2 115	−	−	−	+
JM	60	IV	257	1 257	−	−	+	+
III. *Atypical lentigines*								
CO	45	II	213	910	−	−	+	−
CG	45	III	52	399	+	−	+	−
BR	59	III	290	2 737	+	−	+	−
KI	30	III	55	791	−	−	+	−
AD	70	III	47	219	+	−	+	+
ML	60	IV	172	1 276	−	−	+	+

(1.2%) displayed isolated peculiar hyperkeratoses of a Bowenoid type and similar findings have been described earlier (6). Solitary lesions of actinic keratosis were observed in 2%. Malignant transformation to invasive carcinoma was not seen in any patient.

Another feature not uncommon as a sequel of PUVA treatment is the peculiar mottling and lentiginosis seen after long-term therapy (3, 8, 9, 10, 17). This phenomenon was observed in 33% of our patients and an extremely profuse lentiginosis in 4%. In a special project in this study every possible change of pre-existing nevocellular nevi was followed and any newly developed suspicious dark spot was biopsied. Twenty-one nevi from 18 patients were then excised and processed for light microscopy and electron microscopy. The findings were described in a previous report by Lagerholm & Frithz (9). No convincing signs of malignancy were observed, although the structural organization of the melanosomes was polymorphous and profoundly aberrant.

The lentiginosis observed is a quite different phenomenon (cf. Table XI). These spots are freckle-like, light or dark brown in colour, and sometimes widely scattered. The lentiginous maculae are usually regular in outline. Any area of the skin may be involved and the diameter of the hyper-

Table X. *Percentage of skin types I and II and frequency of earlier therapeutic modalities in PUVA-treated patients with actinic elastosis, actinic keratosis and profuse lentiginosis, compared with the frequency in all investigated PUVA patients*

	Skin type I+II (%)	Earlier arsenic therapy (%)	Earlier Grenz rays (%)	Earlier UVB therapy (%)	Earlier MTX therapy (%)
In patients with					
Actinic elastosis	33	50	16	100	16
Actinic keratosis	40	40	60	80	20
Lentiginosis, profuse	20	20	33	100	33
In all PUVA patients investigated (n=250)	10	20	21	91	12

Table XI. *Lentigo simplex compared with atypical lentigo; histopathological and clinical characteristics*

	Lentigo simplex	Atypical lentigo
Micromorphology		
Epidermal pigmentation	Moderate	Heavy
Linear melanocytic interretal proliferation	Rare	Extensive
Pagetoid melanocytic occurrence	Absent	Abundant
Dendritic elongation	Absent	Considerable
Nuclear polymorphism	Absent	Slight
Macromorphology		
Colour	Light or dark brown	Dark brown or black
Outline	Mostly regular	Mostly irregular
Occurrence	Abundant	Sporadic
Profuse lentiginosis	May occur	Not seen
Predominant skin type	Type III	Type III

pigmented macules can vary between 1 and 4 mm. Light microscopically, lentigo simplex often presents a certain increase in epidermal thickness, with a slight elongation of the rete ridges and a more or less pronounced budding associated with an increased number of melanocytes of normal configuration. The amount of melanin is also increased in both melanocytes and in neighboring keratinocytes, especially in the basal layers. The increase in the number of melanocytes is most pronounced in the deep parts of the rete ridges. In lentigo simplex there is no formation of nevus cell nests. If, however, nests of nevocellular cells appear in the epidermo-dermal junction area, this must be interpreted as the occurrence of a nevus incipiens or junctional nevus. Transformation of this kind was not observed in any of our patients.

Atypical lentigo in this connection is defined as clinically and microscopically aberrant lentigines. Clinically the lentigines appeared more or less eruptively during PUVA treatment and had varying diameters. The colour was usually dark brown or black. Microscopically, the atypical lentigines were hyperpigmented and the melanocytes were abundant, often propagating in the basal layer in a linear way within the rete ridges and between these structures. The synthesis of melanosomes was increased (9) and the dendrites elongated. There was an obvious increase in melanin transfer, resulting in hyperpigmentation of the keratinocytes. A Pagetoid distribution of melanocytes was sometimes observed when being more pronounced, creating a configuration similar to atypical melanocytic hyperplasia. The combination of linear hyperplasia and Pagetoid appearance of the melanocytes sometimes created an impression of clustering or nest formation. Mitoses were rare, however. Cytomorphologically, besides the elongation of dendrites, the melanocytes were characterized by a certain nuclear polymorphism. The cytoplasm contained atypical melanosomes (9) although without any predominating type.

The clinical significance of the appearance of atypical lentigines in relation to PUVA therapy seems to be causal, but whether or not those patients stand an increased risk of developing future malignant transformation is not known. Atypical lentigines appeared in 6 patients (2.4%) as solitary lesions; most patients had only a single or a few lesions of this type. Profuse lentiginosis was not a common feature in these patients. They were not of fair, light-sensitive complexion; only one had skin type II, while the others had skin type III or IV. All of them had earlier undergone several courses of extensive UVB treatment and 3 of them were also earlier subjected to arsenic therapy.

It should be noted that in our 10 patients with a profuse disseminated lentiginosis, no atypical lentigines were seen, either clinically or microscopically. Hence it is concluded that very dark irregular lentiginous spots, when appearing during PUVA therapy, should be excised for microscopical judgement. Patients developing atypical lentigines should be referred to the risk group category and future supervision is advised until more is known about this clinical entity.

The present reinvestigation confirms the efficacy of PUVA therapy for severe cases of longstanding psoriasis and no serious side effects have been observed in patients followed for up to 7 years.

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Received June 8, 1982

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