Severely Photosensitive Psoriasis: A Phenotypically Defined Patient Subset

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A subset of patients with chronic plaque psoriasis exhibits severely photosensitive psoriasis (PP) with a pronounced seasonal pattern, but the pathomechanism is not understood. We performed two related studies; first, a detailed clinical characterization of PP, and second, a controlled investigation exploring the underlying pathomechanisms through the assessment of disease onset after photoprovocation. Patients with PP ($n=20$) showed striking female predominance (19F:1M), very low mean age of psoriasis onset (11 years, range 2–24), family history of psoriasis (13/20), a strong HLA–Cw*0602 association (16/17), and a rapid abnormal clinical response to broadband UVA, comprising erythema ± scaling plaques (17/20). Subsequently, patients with PP ($n=10$), non-PP ($n=9$), and healthy volunteers ($n=11$) were challenged with low-dose broadband UVA on 3 consecutive days, and serial biopsies were taken after 6 hours to 7 days and from unchallenged skin. Histological changes consistent with early psoriasis occurred in 4 of 10 PP patients, but in neither of the control groups, with significant dermal infiltration by neutrophils, $CD4^+$, $CD8^+$, and $CD45RO^+$ cells at 24 h, accompanied by acanthosis. Thus, a phenotypically distinct subset of psoriasis has been characterized. In contrast with earlier assumptions, UV can provoke psoriasiform features rapidly *de novo*; a role for memory effector T cells is supported in the early phase.

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INTRODUCTION

Exposure to UVR is usually beneficial in psoriasis, but it is recognized that in a significant minority, estimated between 5 and 20% of patients, psoriasis worsens (Lane and Crawford, 1937; Lomholt, 1963; Farber *et al*., 1968; Ros and Eklund, 1987). The mechanisms underlying this are poorly understood, but are proposed to include Köbnerization after sunburn in fair skin (Bielicky and Kvicalova, 1964; Frain-Bell, 1979) or after polymorphic light eruption (Ros and Eklund, 1987; Ros and Wennersten, 1986), coexistence of other photosensitivity disorders (Millns and Muller, 1980; Doyle, 1984), and direct UVR triggering or exacerbation of psoriasis *de novo*. It is assumed that *de novo* photoprovoked psoriasis takes several days to manifest after UVR, and that a rapid onset of a photosensitive reaction in patients with psoriasis is more likely to denote a coexistent photosensitivity disorder (Ros and Wennersten, 1986).

In our tertiary referral psoriasis clinic, we have identified a subset of patients with severely photosensitive psoriasis (PP), in whom the condition is predominantly photodistributed and is severe in the summer months, whereas it is mild or absent in winter. Moreover, they show a relative ease of provocation by artificial UV sources. This has presented an opportunity both for a detailed characterization of their phenotype and for an examination of the underlying pathomechanisms. First, we performed a detailed clinical characterization of 20 patients identified to have PP. Second, we conducted a controlled study of the histological and molecular responses of PP to low-dose UV provocation, with the challenge selected to avoid risk of Köbnerization as a confounder. Further, we included two control groups to evaluate for any potential influence of the Köbnerization phenomenon or of a nonspecific UV effect. Thus, 10 patients with PP, 9 with chronic plaque psoriasis and no history of UV exacerbation (P), and 11 volunteers with healthy skin (N) were recruited. Sequential skin biopsies were taken after exposure to low-dose broadband (bb)UVA, and evaluated histologically and immunohistochemically. The principal aims of our studies were to clinically characterize this subset of patients with severely PP, to evaluate impressions from our clinical practice that PP could be rapidly and directly provoked by UV, and to explore the role of potential pathogenic T-cell subsets that we hypothesize are key to the early evolution of PP.

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Abbreviations: bbUVA, broadband ultraviolet A; P, psoriasis; PP, photosensitive psoriasis; PPneg, histology negative photosensitive psoriasis; PPpos, histology positive photosensitive psoriasis; UVB, ultraviolet B; UVR, ultraviolet radiation

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RESULTS

Clinical study

Severely PP shows pronounced female preponderance, develops at an early age, and is associated with a positive family history in the majority. Among the 20 patients with PP, there was a striking female bias, with 19 females to one male (Table 1). Two-thirds, that is, 13 of 20 patients, had a positive family history of psoriasis, 7 in first-degree relatives. There was a marked early age of onset for many patients, with 12 of 20 developing psoriasis under 10 years of age. Eleven patients had PP from the outset, whereas others noticed a worsening of their condition after UV exposure later in life; three had even found UV helpful initially. Their psoriasis occurred predominantly on exposed sites (Figure 1) in summer months, with an absent or minimal involvement in winter. Eight required systemic medication for psoriasis, solely or predominantly in the summer. Five of 20 were of skin phototype I.

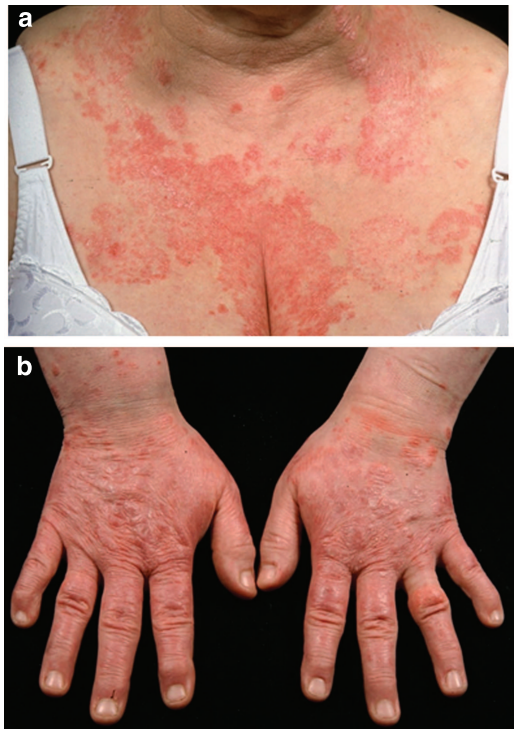

Figure 1. Clinical distribution of psoriasis in PP. (**a**) and (**b**) Photographs of a patient with PP, demonstrating the involvement of photoexposed sites.

Severely PP is associated with HLA–Cw*0602. Of the 17 patients undergoing HLA typing, 2 were homozygous positive for HLA–Cw*0602 and 14 were heterozygous, indicating a strong association with this allele. No specific pattern of the HLA–DRB1* distribution was noted, and no patient carried the HLA–DRB1*0407 allele associated with photosensitivity, namely, actinic prurigo.

Monochromated light testing shows normal minimal erythema doses to narrowband UVB, UVA, and visible radiation, whereas broadband UVA provocation elicits a rapid abnormal clinical response in the majority of patients with severely PP. Monochromator light testing revealed normal responses to narrow bandwidths of UVB, UVA, and visible light in all but one patient tested; the latter had a slightly lowered erythemal threshold of 14 J cm^{-2} to UVA at 370 nm. Broadband UVA provocation testing was abnormal in 17 of the 20 patients, comprising macular erythema, sometimes accompanied by small scaly plaques consistent with psoriasis (Figure 2). Two of the three patients with negative provocation were taking systemic medication during photoinvestigation (1 hydroxycarbamide, 1 fumarate), which may explain their negative results. Nine patients were exquisitely sensitive to bbUVA on testing and developed visible cutaneous features after only one exposure to bbUVA at 20 J cm^{-2}. Three patients developed a papular erythema clinically consistent with polymorphic light eruption. Serum investigations showed a weakly positive antinuclear antibody in four patients (titer 1 in 100), moderately positive in one (titer 1 in 1000), and normal porphyrin levels in all.

Controlled pathomechanistic study

Repeated broadband UVA challenge induces abnormal clinical reactions in severely PP but not in non-PP or healthy controls. Age, sex, and clinical severity of psoriasis (PASI score) were very similar between the groups (Table 1), and similar antinuclear antibody positivity prevalence was noted

Table 1. Demographic and psoriasis severity data[1] for participants at the time of study assessment

			Photosensitive psoriasis (PP)		
			PP biopsy group		
	Healthy volunteer	Non-photosensitive psoriasis	Histology positive (PPpos)	Histology negative (PPneg)	All
No. of participants	11	9	4	6	20
Sex	8F, 3M	7F, 2M	4F	5F, 1M	19F, 1M
Age (years)	42 (24–58)	44 (31–58)	42 (19–62)	41 (20–65)	45 (19–74)
Age at onset of psoriasis (years)	NA	25 (5–48)	12 (8–18)	11 (4–23)	11 (2–24)
PASI	NA	4.6 (2.4–6.8)	4.3 (1.2–8.9)	5.5 (3.4–8.2)	NA
Skin phototype I (number)	1	0	0	2	5

[1]Data are mean (range); NA, not applicable.

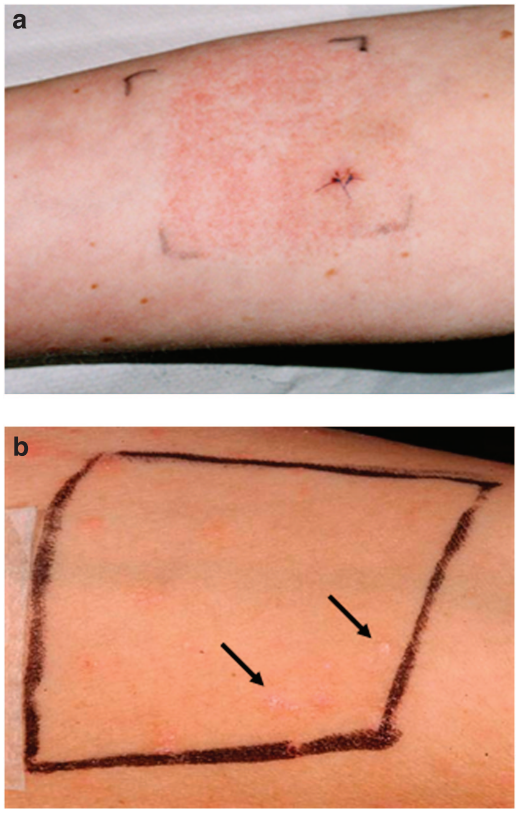

Figure 2. Provocation response of PP to UVA exposure. UVA exposure induces visible clinical change in PP, which can manifest as (**a**) macular erythema, 24 hours after final UVA exposure and (**b**) new scaly erythematous lesions consistent with psoriasis, shown 1 week after final UVA exposure (arrows).

in all groups. All 10 patients with PP developed visible abnormal responses after bbUVA challenge to the forearm, comprising macular erythema ± scaling, but in comparison, among the controls ($n = 20$), one healthy volunteer and one non-PP patient showed only faint transient erythema after the third bbUVA challenge.

Broadband UVA induces acanthosis, neutrophilic infiltration, and specific changes in CD4$^+$, CD8$^+$, and CD45RO$^+$ T lymphocytes in a proportion of patients with PP. Histological features consistent with early psoriasis were seen in 4 of 10 patients with PP (Figure 3). These included acanthosis accompanied by an infiltrate of neutrophils and lymphocytes. No histological changes were observed in other patients after bbUVA exposure. Histology-positive PP (PPpos) patients were therefore assessed separately from those with histology-negative PP (PPneg).

At 7 days after UV exposure, an overall between-subject-group difference was seen in epidermal thickness ($P < 0.05$). The PPpos group showed a trend for epidermal thickening with time after bbUVA exposure ($P = 0.05$, Supplementary Figure S1).

A significant increase in dermal neutrophilic infiltrate developed in the PPpos group in comparison with the PPneg group, the healthy skin group, and the non-PP group at 24 hours after bbUVA exposure, all $P < 0.05$ (Figure 4).

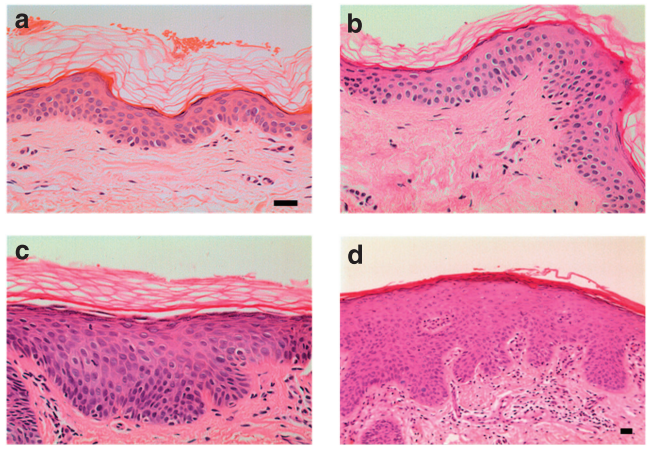

Figure 3. UVA-induced histological changes in PP. Photomicrographs of hematoxylin-eosin-stained sections after UVA provocation at (**a**) baseline; (**b**) 24 hours; (**c**) 7 days. Images (**b**) and (**c**) show UVA-induced histological features consistent with early psoriasis, including epidermal thickening and inflammatory cell infiltrate and (**d**) shows typical features of psoriasis, including psoriasiform hyperplasia, parakeratosis, dermal papillary vessel dilatation, and inflammatory cell infiltrate in a fully evolved psoriatic plaque from the same patient. Scale bars = 100 μm.

The most notable changes in the T lymphocyte subsets were observed 24 h after the final bbUVA provocation, with significant between-group differences in CD4$^+$, CD8$^+$, and CD45RO$^+$ T cells, whereas no significant difference was observed in natural killer cells (CD56). Marked early (24 hours) increases in dermal CD4$^+$, CD8$^+$, and CD45RO$^+$ cells were observed in the PPpos group in comparison with the control groups ($P < 0.05$), whereas CD8$^+$ cells were significantly higher in the PPpos group than the healthy group at baseline ($P < 0.05$), and significantly higher at 7 days in PPpos than in each of the other groups ($P < 0.05$, Figure 5).

DISCUSSION

We have phenotypically characterized a subset of severely PP patients. The disorder, which we identified according to the striking seasonal pattern of the psoriasis, that is, severe during summer months and mild/absent during winter, accompanied by a predominant involvement of sun-exposed sites, shows behavior more analogous to a photosensitivity disorder than to the more often witnessed, modestly photoaggravated psoriasis. Accompanying this severely photosensitive pattern of psoriasis, our patient group exhibits the following key features: (i) a striking female predominance (19 of 20) and a very young mean age of onset of psoriasis (11 years), with a synchronous development of the photosensitivity component in some patients (11 of 20); (ii) essentially normal minimal erythema doses to UVB, UVA, and visible light on monochromated light testing; and (iii) ease of provocation of abnormal clinical responses to low-dose bbUVA, with, in some instances, the rapid development of psoriasiform features, contrasting with previous assumptions with regard to the behavior of UV-sensitive psoriasis.

Previous studies of patients with psoriasis showing sensitivity to sunlight were performed in less well-defined

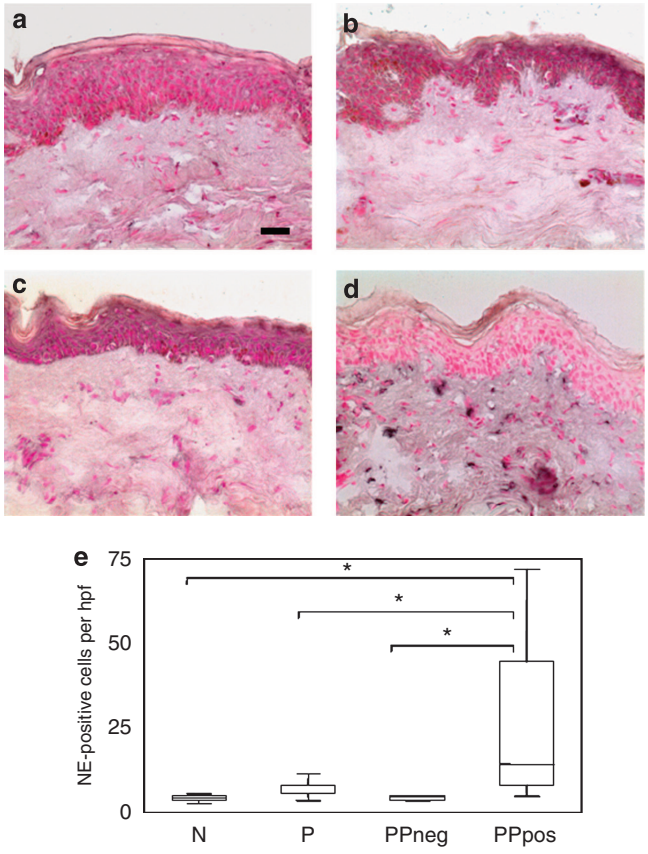

Figure 4. Dermal neutrophilic infiltration 24 hours after final UVA provocation. Snap-frozen samples were cut in 10 µm sections, fixed in PFA, and immunostained with a mouse anti-human neutrophil elastase primary antibody. Dermal positively staining cells were manually counted on 9 high-power (× 400 magnification) fields. (**a**) Healthy volunteer (N), (**b**) non-photosensitive psoriasis (P), (**c**) histology-negative photosensitive psoriasis (PPneg), (**d**) histology-positive photosensitive psoriasis (PPpos). Scale bar = 100 µm. (**e**) Dermal neutrophilic infiltration was significantly higher in the PPpos group in comparison with that in the PPneg group and in control groups at 24 hours after bbUVA exposure. Data are median, interquartile range, and range; $*P<0.05$.

patient groups and likely included several diagnostic entities including psoriasis with a modest light aggravation, that is, ''photoaggravated psoriasis''. Nevertheless, a female preponderance (Lomholt, 1963; Bielicky and Kvicalova, 1964; Ros and Eklund, 1987) and positive family history (Ros and Eklund, 1987) have been reported, with early disease onset in some (Bielicky and Kvicalova, 1964) but not all studies (Ros and Eklund, 1987). Early reports regarding photoaggravated psoriasis suggested that most were due to Köbnerization in fair-skinned patients, with reports of reduced erythemal thresholds to UVB in some patients (Bielicky and Kvicalova, 1964; Frain-Bell, 1979; Ros and Wennersten, 1986). However, only 5 of 20 of our PP patients had skin phototype I, and all had normal erythemal thresholds to UVB. We selected low-dose bbUVA in preference to a UVB source for provocation testing in this study to avoid confusion due to the elicitation of psoriasis through Köbnerization; future studies might cautiously explore the impact of UVB challenge. Ros and Wennersten (1986) reported coexistent polymorphic light eruption in 18 of 35 patients with photoaggravated psoriasis, and others reported photoaggravated psoriasis in association with chronic actinic dermatitis (Fujii *et al.*, 2002; Sahoo and Kumar, 2002) and lupus erythematosus (Millns and Muller, 1980; Doyle, 1984). However, although features of polymorphic light eruption were witnessed in three PP patients, we found no evidence of any other coexisting photosensitivity disorder.

Our PP patients show some similarities with type 1 psoriasis, namely, early disease onset, positive family history, and association with HLA-Cw6 (Henseler and Christophers, 1985). Notably, >90% of PP patients carried the HLA–Cw*0602 allele, compared with ~60% of patients with early-onset psoriasis and 15% of healthy controls (Gudjonsson *et al.*, 2006); HLA-Cw6 is not associated with late-onset psoriasis (Allen *et al.*, 2005). Intriguingly, one study mentions that HLA-Cw6-positive psoriasis patients are more likely to report a beneficial effect of sunlight, but details of these findings are lacking (Gudjonsson *et al.*, 2002). The sex ratio of our PP patients notably contrasts with non-photosensitive early-onset psoriasis, in which the ratio is approximately equal (Young *et al* 2004). The striking female predominance in PP (95% of our group) is concordant with the observation that the majority of patients diagnosed with photosensitivity in photobiology units are female. Experimental data indicate that estrogens can prevent UVB-induced immunosuppression (Hiramoto *et al* 2004, Widyarini *et al* 2006) and that UVA can reverse UVB-induced immunosuppression through estrogen receptors (Cho *et al* 2008). This requires a study in humans, but it is conceivable that females are more resistant to photoimmunosuppression and are thus more sensitive to the photoactivating effects of UVA in certain photosensitivity disorders, potentially including PP.

In our controlled study, prominent histological changes were observed in biopsies from 4 of 10 PP patients, whereas a clinical response was observed in all 10 PP patients. The protocol used a low-dose, repeated UVA challenge to investigate an early evolution of PP and avoided a higher dose of UVA or UVB that might produce sunburn and subsequent Köbnerization; this approach is supported by negative responses in our control groups. The P and PP groups were very similar in characteristics, except for the photosensitivity and the very young age of psoriasis onset in PP (Table 1). We propose that the latter is an intrinsic feature of PP and that the age of onset of the disorder is unlikely to influence provocation outcome. The macular, sometimes scaling, erythema we observed in PP thus seems to be a pathological reaction to UVA, whereas the challenge may be insufficient to fully provoke psoriasis. The histological changes we observed, namely, acanthosis and neutrophilic and lymphocytic infiltration, are typical early findings in psoriasis. Acanthosis is believed to be secondary to immune dysregulation, with stimulation by the Th17 cytokine IL-22, which mediates the effects of IL-23 (Zheng *et al.*, 2007; Ma *et al.*, 2008). A neutrophilic infiltration of epidermis and dermis is observed in both early and established plaques of psoriasis (van de Kerkhof, 2007). We found significant $CD4^+$, $CD8^+$, and $CD45RO^+$ lymphocyte infiltration a

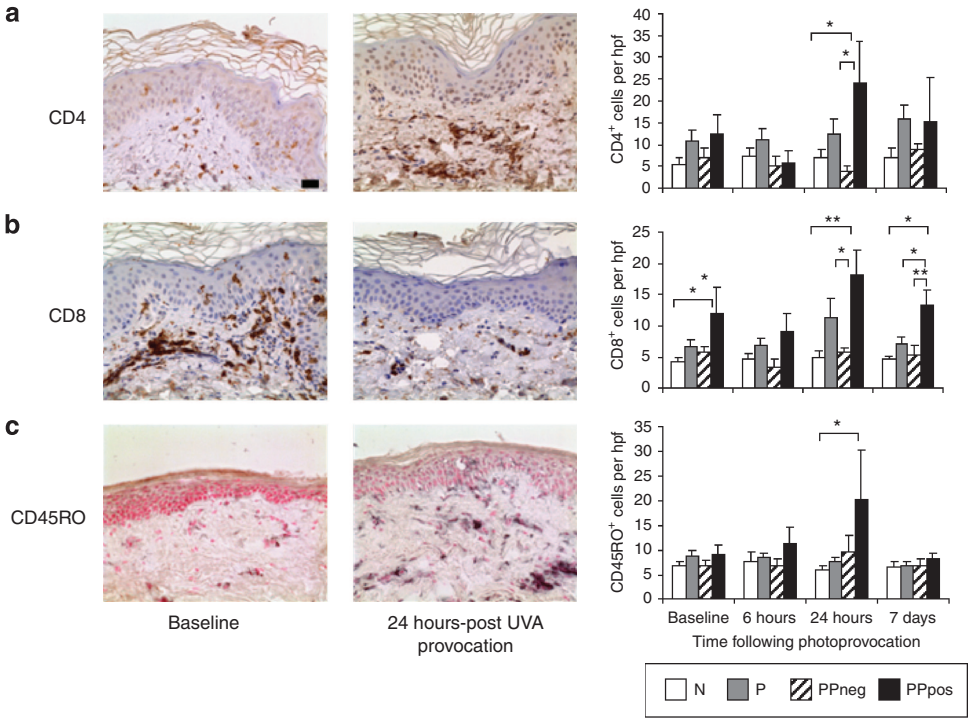

Figure 5. Dermal T-lymphocyte subset infiltration after UVA provocation, showing (a) $CD4^+$-, (b) $CD8^+$-, and (c) $CD45RO^+$-staining cells. For CD4 and CD8 analysis, formalin-fixed and paraffin-embedded samples were sectioned 3–4 μm thick and immunostained using a standard method. Acetone-fixed 10 μm sections were immunostained with primary antibody for CD45RO analysis. Positively staining dermal cells were manually counted on 9 high-power (×400 magnification) fields. Dermal $CD4^+$ and $CD8^+$ counts were significantly higher in the PPpos group compared with those in the PPneg and N groups 24 hours after UVA exposure, and $CD8^+$ counts were significantly higher in PPpos than in all other groups at 1 week after UVA exposure. $CD45RO^+$ counts were significantly higher in PPpos than in healthy individuals at 24 hours after UVA exposure. Scale bar = 100 μm. Data are mean and SEM; $*P<0.05$, $**P<0.01$.

maximum of 24 hours after the final UVA provocation. Plaques of psoriasis are characterized by pathogenic T-cell subsets, predominantly $CD4^+$ cells in the dermis and $CD8^+$ cells in the epidermis (Bos *et al.*, 1989; Bovenschen *et al.*, 2005). The majority of T lymphocytes in psoriasis are $CD45RO^+$ memory effector cells (Bos *et al.*, 1989; Morganroth *et al.*, 1991); these may have a key pathomechanistic role (Griffiths, 2003; Vissers *et al* 2004; van de Kerkhof, 2007). Our study supports their early involvement in the evolution of PP.

In summary, we have characterized a group of patients with psoriasis who show profound impact of season, striking female preponderance, early onset of disease, and ease of provocation of clinically abnormal changes after low-dose UVA. The challenge was sufficient to provoke psoriatic lesions in some individuals, demonstrating that psoriasis can develop rapidly and directly after UV exposure. Histology supports the diagnosis of psoriasis and indicates a role for memory effector T cells in the early phase. This uncommon but phenotypically distinct subset of psoriasis deserves further attention.

MATERIALS AND METHODS

Participants

Clinical/photobiological study. The participants ($n=20$) were patients with chronic plaque psoriasis attending the psoriasis clinic of the Dermatology Centre, Salford Royal NHS Foundation Hospital, Manchester, between November 2003 and April 2005, who were identified to have severely PP as follows: a routine clinical questionnaire of 340 psoriasis patients indicated 38 with a positive response to the question "Is your psoriasis made worse by sunlight?" After an interview, 20 of the 38 patients were classified as having PP on the basis of a history of psoriasis predominantly affecting sun-exposed sites, which was severe in summer but minimal or absent in winter; thus, patients with a milder element of photoaggravation were excluded.

Controlled pathomechanistic study. Ten of the PP patients who participated in the above clinical study volunteered to participate in the subsequent controlled investigative study. Nine non-photosensitive chronic plaque psoriasis (P) patients were recruited from the same psoriasis clinic as were the photosensitive patients after a negative clinical questionnaire response regarding sunlight sensitivity. In addition, 11 healthy volunteers with normal skin (N) were recruited after a poster advertisement.

The exclusion criteria for volunteers in both studies were pregnancy, lactation, age <18 years and >75 years, and the use of photosensitizing medication. Two patients were not included in the analysis: one healthy volunteer who unexpectedly took medication with photosensitizing potential and who developed confluent erythema after 3 consecutive days of UVA provocation, and one patient with non-PP who developed an acute contact dermatitis reaction to dressings. The study was approved by the Salford and Trafford Research Ethics Committee and was conducted according to the Declaration of Helsinki principles. Participants gave their written informed consent.

Photobiological study of PP patients

A detailed photoinvestigation was performed in the Photobiology Unit of the Dermatology Centre. Nineteen patients with PP underwent monochromated light testing (High Intensity Monochromatic System, L.O.T.- Oriel Ltd, Surrey, UK) on the skin of the mid-back with narrow bandwidths of UVB, UVA, and visible radiation at 300, 320, 330, 350, 370, 400, 500, and 600 nm (bandwidth 5 nm at 300 nm, 20 nm at all other wavelengths). Minimal erythemal doses were read at 24 hours. All 20 PP patients received bbUVA provocation testing (TL09, Philips Lighting UK, Guildford, UK, 313–370 nm), with exposure of a 5 cm^2 area of ventral forearm skin to 20 J cm^{-2} UVA over 1–3 consecutive days. The site was examined at 24 hours after each challenge. This low dose was chosen to avoid the possibility of Köbnerization and the challenges were discontinued once an eruption was provoked. Blood samples were taken for antinuclear antibody and extractable nuclear antigens, and blood and urine samples were taken for porphyria screening. HLA testing was carried out on 17 PP patients for associations relevant to psoriasis (Cw6) and photosensitivity (DR4 typing, including DRB1*0407).

Controlled pathomechanistic study

Ten of the PP patients from the photobiological study were further involved in an investigative mechanistic study, together with 20 controls (9P, 11N). Control individuals were interviewed to ensure that they had no history of photosensitivity. Blood samples were taken for antinuclear antibody and extractable nuclear antigens. All volunteers received bbUVA provocation to their ventral forearm skin on 3 consecutive days, as described for the photobiological study. A series of four punch skin biopsies were taken from the bbUVA-exposed forearm skin at (i) baseline (clinically normal skin before provocation); (ii) 6 hours after the first UVA provocation; and (iii) 24 hours and (iv) 1 week after the final UVA provocation. The biopsies were bisected and half formalin fixed and half snap-frozen in an optimal cutting temperature medium (Tissue-Tek; Miles, IN) before storage at −80 °C.

Histology and immunohistochemistry

The samples underwent hematoxylin and eosin staining and microscopic assessment by a dermatopathologist (TB) blinded to the study. Epidermal thickness was measured microscopically by image analysis (Leica Qwin; Leica Microsystems GmbH, Wetzlar, Germany), with 10 measurements taken on each section. For CD4 and CD8 analysis, formalin-fixed and paraffin-embedded samples were sectioned 3–4 μm thick and dried at 58 °C overnight onto adhesive-coated slides. The sections were immunostained using a standard method. Antigen retrieval was carried out using a microwave in 0.01 M Tris-EDTA at pH 8.5. A primary antibody was applied to the slides: CD4 (clone 1F6; Novocastra, Newcastle upon Tyne, UK), dilution 1 in 50, and CD8 (clone C8/144B; Dako SA, Glostrup, Denmark), dilution 1 in 25, each for 30 minutes at room temperature. Detection and visualization was by using the polymer-peroxidase-DAB method (REAL EnVision, Dako UK Ltd, Ely, UK), used according to the manufacturer's recommendations, on a Dako autostainer. Nuclei were stained with Harris' hematoxylin.

Other immunohistochemical analyses were conducted on frozen sections. Sections (10 μm) were fixed in chilled acetone (CD45RO) or 4% paraformaldehyde (CD56, neutrophil elastase). In brief, the sections were washed in tris-buffered saline before solubilization (0.1% (v/v) Triton-X in tris-buffered saline) and treated with 0.6% (v/v) hydrogen peroxide in methanol (30 minutes) to block endogenous peroxidase activity. Nonspecific binding was minimized by incubation with bovine serum albumin/normal serum (1–3% in tris-buffered saline; 60 minutes, room temperature), followed by overnight incubation at 4 °C with a primary antibody (CD45RO, clone UCHL1, Dako SA; CD56, clone M7304, Dako SA; neutrophil elastase, MAB1056, Chemicon, Chandlers Ford, UK). Staining was visualized using a standard peroxidase methodology (Vector ABC *Elite*, Vector Laboratories, Peterborough, UK), using Vector SG as chromogen. The sections were counterstained with nuclear fast red (Vector), washed, dehydrated, and mounted with DePex (BDH, VWR International, Lutterworth, UK). The stained sections were blinded and randomized before manual counts of positive cells (9 hpf, × 400 magnification, per volunteer per time point).

Statistical methods

Data are reported as mean (± SEM). Overall between-group differences were tested using analysis of variance, and the *post hoc* Tukey method or the two-sample *t*-test was used to assess statistical significance between two groups. Fisher's exact test was used to test categorical variables. $P<0.05$ was considered to be statistically significant. SPSS version 15.0 (SPSS Inc., Chicago, IL) was used for the analysis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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