

Distribution of Naive and Memory T-cells in Photoproved and Spontaneous Skin Lesions of Discoid Lupus Erythematosus and Polymorphous Light Eruption

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Immune response to ultraviolet radiation-modified skin antigens has been suggested as a pathomechanism of skin lesions in discoid lupus erythematosus and polymorphous light eruption. In order to elucidate the role of T-lymphocyte subsets in this response, we studied the distribution of CD45RO⁺, CD45RA⁺ and CD31⁺ cells and the endothelial expression of adhesion molecules E-selectin/P-selectin, intercellular adhesion molecule-1 and CD31 antigen in photoproved and spontaneous skin lesions. Typically, CD45RA⁺ cells were the prevailing inflammatory cell population of discoid lupus erythematosus, whereas CD45RO⁺ cells prevailed in both diseases and in healthy controls. Epidermotrophism of any T-cell subsets was more typical of discoid lupus erythematosus, whereas no major differences in endothelial adhesion molecule expression was found between the 2 diseases. Strong keratinocyte ICAM-1 expression was associated with adjacent CD45RO⁺ cell infiltrates, not with CD45RA⁺ or CD31⁺ cell infiltrates. We conclude that the cellular immune response to UV radiation is dissimilar in discoid lupus erythematosus and polymorphous light eruption. Key words: CD45RO⁺ cells; CD45RA⁺ cells; CD31⁺ cells; helper inducer; suppressor inducer.

(Accepted May 20, 1999.)

Acta Derm Venereol 1999; 79: 437–442.

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It is well-known that ultraviolet radiation (UVR) induces and/or aggravates skin lesions in both discoid lupus erythematosus (DLE) and polymorphous light eruption (PLE). However, the exact pathomechanism of UVR-induced skin lesions in either of these disorders is not known, although an autoantigen-specific T-cell-mediated mechanism has been proposed in both (1–2). In addition, our recent finding that 41% of DLE patients have experienced PLE symptoms, most of them prior to DLE (3), suggests an association between the 2 diseases.

Dermal perivascular and perifollicular CD4⁺ (T-helper) cell infiltrations are typically found in skin lesions of both spontaneous and photoproved DLE and PLE (1, 4–6). The migration of these lymphocytes from the vasculature into the skin is thought to be regulated by a specific cascade of several adhesion molecules (7) and epidermal intercellular adhesion molecule-1 (ICAM-1) have been suggested to attract these inflammatory cells further towards the epidermis (8). On the basis of CD45 isoforms, CD4⁺ T-cells are divided into CD45RA⁺ (suppressor inducer) cells, demonstrating functional characteristics of naive T-lymphocytes, not responding to recall antigens, and to CD45RO⁺ (helper inducer) cells

demonstrating functional characteristics of memory cells and responding to recall antigens (9–11).

In order to elucidate eventual differences in the pathomechanism of evolving skin lesions in DLE and PLE patients in relation to UVR exposure, we examined the distribution and accumulation kinetics of the above-mentioned T-lymphocyte subsets. In addition to UVR-provoked skin lesions, spontaneously evolved skin lesions from sun-exposed skin of both DLE and PLE patients were also examined. We also studied the expression of CD31 antigen (platelet/endothelial cell adhesion molecule-1, PECAM-1), since it is proposed to be another marker for naive T-helper cells (12). We compared these findings with those obtained from photoproved skin of healthy control persons, since in healthy human skin, UVR is found to induce a selective influx of non-activated memory T-cells into both dermis and epidermis (13).

We also studied the expression of different endothelial and/or epidermal adhesion molecules in the microenvironment providing T-cell migration from the circulation to the target site in the inflammatory tissue. Thus, E-selectin/P-selectin, a ligand for skin homing T-cells (14), intercellular adhesion molecule-1 (ICAM-1), involved in a firm leukocyte adhesion in inflammatory skin disorders (7) and CD31 antigen, involved in transmigrating the cells through the endothelium (15), were examined.

PATIENTS AND METHODS

Patients

The study group comprised 2 male and 8 female DLE patients (mean age 40 years, range 14–78 years), and 9 female PLE patients (mean age 38 years, range 12–52 years), who had been followed-up at the Department of Dermatology in Tampere University Hospital, Tampere, Finland (Table I). The diagnoses of DLE and PLE were based on generally accepted clinical, (immuno)histological and serological findings (16). Four DLE patients had also experienced PLE-like symptoms. As controls, 13 healthy medical students or members of hospital staff, without any history of photosensitivity, volunteered (7 men, 6 women, mean age 30 years, range 16–42 years).

Photoprovocation

Eight DLE patients, 6 PLE patients and 5 control persons (Table I) were UVA-provoked with UVASUN 3000 (emission spectrum 340–400 nm) and UVB-provoked with Philips TL 20W/12 (emission spectrum mainly 280–370 nm), as described previously (17). The provocation was performed on intact upper back, upper arm or forearm skin, of 5 × 8 cm skin area, during 3 consecutive days after the minimal erythema dose (MED) for both UVA and UVB were determined. Individual UVR doses used in patients and control persons were 10–100 J/cm² (maximally 2 MEDs) of UVA and 1.3–2 MEDs of UVB. The mean total doses of UVA and UVB varied from 293 to 300 J/cm² and from 4.8 to 5.3 MEDs, respectively. The

Table I. Number of patients, skin sites and biopsies examined

	Patients examined	Patients with a pathological photoprovocation reaction	Skin sites examined immunohistologically ^a	Skin biopsies examined immunohistologically
DLE	10		17	24
photoprovoked	8	4	6 ^b	13
not photoprovoked	2		9 ^c	9
not photoprovoked	2		2 ^d	2
PLE	9		13	14
photoprovoked	6	5	6 ^e	7
not photoprovoked	3		3 ^c	3
not photoprovoked	3		4 ^f	4
Control persons	13		20	20
photoprovoked	5	0	10 ^c	10
not photoprovoked	8		10	10

^aFrom 4 DLE patients and 1 PLE patient, serial biopsies were obtained.

^bDLE-like, infiltrated, long-lasting photoprovocation lesions, 2 with UVA and 4 with UVB.

^cNormal photoprovocation reaction with short-lasting erythema eventual slight oedema or pigmentation.

^dSpontaneous DLE lesions, less than 3 weeks of duration from the previously sun-exposed skin.

^ePLE-like, papular or papulovesicular photoprovocation lesions, 3 with UVA and 3 with UVB.

^fSpontaneous PLE lesions, less than 10 days of duration from the previously sun-exposed skin.

DLE=discoid lupus erythematosus, PLE=polymorphous light eruption.

procedure was approved by the ethics committee of the hospital and was performed, after informed consent, during 3 consecutive days. The test areas were evaluated about 24 h after each irradiation and thereafter every 4–7 days for up to 3–6 weeks. Any erythematous papular/vesicular or plaque photoprovocation reaction was considered pathological. Erythema, and eventual slight oedema, disappearing within 3 days, as well as pigmentation were considered normal (17).

Immunohistochemical and histological studies of skin biopsies

A biopsy was obtained for immunohistochemical studies from DLE- and PLE-like lesions as soon as a clinically pathological UVA- or UVB-provoked reaction was seen. Serial biopsies were further obtained 2 or 3 times at approximately 7-day intervals as long as the lesion persisted. The mean interval between the last provocation and the biopsy was 11 days (range 1–31 days) in DLE patients, 3 days (range 1–8 days) in PLE patients and 7 days (range 6–7 days) in control persons. The short mean interval in PLE patients was due to the short duration of the skin rash. In addition, spontaneous DLE and PLE lesions from sun-exposed skin, non-lesional UVA- and UVB-provoked skin from both patients and control persons and non-UVR-exposed intact skin of healthy control persons were examined (Table I).

The biopsy specimens were snap-frozen in liquid nitrogen and stored at -70°C until analysis. The avidin-biotin peroxidase technique, using a Vectastain Elite ABC kit (Vector Laboratories, Burlingame, CA, USA), was used for immunohistochemistry. Briefly, 5- μm thick cryostat sections were fixed in cold acetone followed by chloroform, and blocked with normal horse serum. The sections were then incubated with primary mouse monoclonal antibodies, diluted in 0.01 mol/l phosphate-buffered saline containing 0.1% bovine serum albumin, followed by biotinylated secondary antibody. The following monoclonal antibodies were used: CD4 (OKT-4A, Ortho Diagnostic Systems Inc. Raritan, NJ, USA) dilution 1:10, CD8 (Leu 2a, Beckton-Dickinson, San Jose, CA, USA) dilution 1:100, CD22 (isotype IgG₁ kappa, a marker for B-cells, Dako, Glostrup, Denmark) dilution 1:100, CD45RO (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB), Amsterdam, the Netherlands) dilution 1:30, CD45RA (CLB) dilution 1:15, CD31 (platelet/endothelial cell adhesion molecule-1, CLB) dilution 1:200, CD54 (ICAM-1, R&D Systems, Abingdon, UK) dilution 1:2000, CD62E/CD62P (E-selectin/P-selectin, R&D Systems) dilution 1:2000. After quenching the endogenous peroxidase with 0.3% H₂O₂ in methanol, the sections were incubated with an avidin-biotin

peroxidase complex. The reaction was visualized with diaminobenzidine and the slides were counterstained with haematoxylin.

The immunostained sections were examined independently by 2 of the authors (TH and AR), blinded to identity and time-point of the biopsy. The overall infiltration of inflammatory cells was graded as scanty, moderate, strong or very strong. As counting of the exact number of inflammatory cells was considered insufficiently accurate in most frozen specimens, the proportional quantity of the cells was estimated and marked as + if $\leq 25\%$, ++ if 26–50%, +++ if 51–75% and ++++ if 76–100% of the infiltrating mononuclear cells stained positively. For statistical analysis, the values were scored from 1 to 4, respectively. Intraepidermal infiltration of inflammatory cells was graded as scattered, focal or wide. Endothelial cell staining was graded as weak (=1), moderate (=2), strong (=3) and very strong (=4). In order to grade the epidermal (keratinocyte) ICAM-1 staining, the scores of 4 variables were added: (i) intensity of the reaction; (ii) quantity of positive cells on the horizontal; and (iii) vertical axes of the section (each scored from 0 to 3) and (iv) type of the staining, which was either intracellular (scored as 1) or membranous (scored as 2). Summing up the scores, 4 or 5 were graded as weak, 6 or 7 as moderate, 8 or 9 as strong and 10 or 11 as very strong staining.

Biopsy specimens for routine histological evaluation were obtained from 6 UVA- or UVB-provoked or spontaneous DLE lesions and from 10 UVA- or UVB-provoked or spontaneous PLE lesions simultaneously with the biopsies for immunohistology.

Statistical analysis

For comparing the proportional quantity of T-cell subsets in different patient and control groups and the associations of strong epidermal expression of CD54 (ICAM-1) to different T-cell subsets, Fisher's exact test (2-tailed) was used and performed with Statistica[®] for Windows (Version 5.1, StatSoft Inc, Tulsa, Okla, USA). Values of $p < 0.05$ were considered statistically significant.

RESULTS

Inflammatory cell subtypes in photoprovoked and spontaneous lesions of DLE and PLE

Six of 8 DLE lesions and 10 of 13 PLE lesions (photoprovoked or spontaneous) were examined histologically. All 6

DLE lesions fulfilled the criteria of LE histology. In the PLE lesions, a PLE-like histology was seen in 4 biopsies, whereas 6 biopsy specimens showed unspecific perivascular dermatitis, often seen as the only histopathological finding in PLE (16).

In photoproved or spontaneous DLE and PLE lesions, CD4⁺ T-cells were the prevailing cell population of the inflammatory cell infiltrations (>50% of the cells positive for CD4 antigen) and outnumbered CD8⁺ cells in all DLE and PLE lesions examined for these markers. Sparse CD22⁺ cells (representing B-lymphocytes) were found only occasionally among mononuclear cell infiltrates in 7 biopsy specimens examined (5 DLE and 2 PLE lesions, either photoproved or spontaneous).

Of the CD45 subsets, CD45RA⁺ cells were the prevailing cell population almost only in DLE lesions, whereas CD45RO⁺ cells prevailed in most skin samples in both patients and control persons (Table II). CD31⁺ cells did not clearly dominate in the inflammatory infiltrates of any patient or control group, although they tended to be somewhat more numerous in DLE lesions than in other samples studied (Table II).

In DLE lesions, CD45RO⁺, CD45RA⁺ and CD31⁺ cells were seen as subepidermal band-like or intraepidermal infiltrates in 60–100% of the biopsy specimens. These patterns were statistically less frequent in PLE lesions, found in 9–46% of the biopsy specimens (*p*-values ranged from 0.0005 for intraepidermal CD45RO⁺ cells to 0.0384 for subepidermal CD31⁺ cells). Furthermore, in PLE lesions with subepidermal band-like cell infiltration, typically dermal papillae (besides perivascular spaces) were invaded, while a more dispersed and continuous infiltration was seen in DLE lesions. Subepidermal band-like or intraepidermal cell infil-

trates were not found in any non-lesional photoproved skin of patients or controls. In serial biopsies from DLE lesions, it was illustrated that CD45RO⁺ cells tended to infiltrate the epidermis and subepidermal area earlier than CD45RA⁺ and CD31⁺ cells. Thus, in all 5 biopsy specimens taken earlier than 9 days after provocation, intraepidermal or band-like subepidermal infiltration of CD45RO⁺ cells was found, whereas corresponding locations of CD45RA⁺ and CD31⁺ cell infiltrations were found in only 1 and 3 specimens, respectively. Intraepidermal or band-like subepidermal infiltration of CD45RO⁺ cells persisted in all 10 biopsy specimens taken later than 9 days after the provocation. During such a later time-point, also CD45RA⁺ (9 of 10 biopsy specimens examined) and CD31⁺ cells (all 10 biopsy specimens examined) were found as intraepidermal or band-like subepidermal infiltrations.

In neither DLE nor PLE lesions, clear-cut differences in relation to UVA or UVB exposure in the dermal or epidermal invasion of the cell types examined were found. Neither were there any major differences in cellular immune response between spontaneous and UVR-induced skin lesions in either diseases. The low number of spontaneous lesions did not permit any statistical comparisons, however (data not shown).

Endothelial E-selectin/P-selectin, ICAM-1 and CD31 antigen expression and association of epidermal ICAM-1 expression to inflammatory cell subtypes

The endothelial expression of E-selectin/P-selectin and ICAM-1 was upregulated in photoproved skin sites in both patients and control persons (data not shown). The median

Table II. Percentage of CD45RA⁺, CD45RO⁺ and CD31⁺ cells among all inflammatory cells in skin samples of DLE, PLE and controls. The numbers denote samples

	UV-provoked or spontaneous DLE lesions (n=15)	Non-lesional UV-provoked skin in DLE patients (n=9)	UV-provoked or spontaneous PLE lesions (n=11)	Non-lesional UV-provoked skin in PLE patients (n=3)	UV-provoked healthy skin (n=10)
CD45RA ⁺ cells					
76–100%	5	0	0	0	0
51–75%	8	0	1	0	0
26–50%	2	4	5	2	2
0–25%	0	5	5	1	8
	<i>p</i> =0.0000 ^a (DLE lesions/non-lesional UV-provoked skin in DLE)				
	<i>p</i> =0.0002 (DLE/PLE lesions)				
	<i>p</i> =0.0000 (DLE lesions/healthy skin)				
CD45RO ⁺ cells					
76–100%	15	3	2	0	1
51–75%	0	2	8	3	8
26–50%	0	1	1	0	1
0–25%	0	3	0	0	0
	<i>p</i> =0.0119 (DLE lesions/non-lesional UV-provoked skin in DLE)				
CD31 ⁺ cells					
76–100%	3	0	0	0	0
51–75%	3	3	3	1	1
26–50%	8	6	4	1	0
0–25%	1	0	4	1	9

^aFor statistical analysis (Fisher's exact, 2-tailed) the values of 0–25% and 26–50% were pooled and those of 76–100% and 51–70%, respectively. All the different groups were compared statistically with each other, except for the group "non-lesional UV-provoked skin in PLE patients", which was excluded due to the small number of samples. Only the statistically significant *p* values between different groups are shown. DLE=discoid lupus erythematosus; PLE=polymorphous light eruption.

grade of endothelial E-selectin/P-selectin staining was strong (grade 3) and that of ICAM-1 and CD31 antigen moderate (grade 2) in both DLE and PLE lesions. Thus, no clear differences in endothelial adhesion molecules examined were observed between DLE and PLE.

When evaluating the relationship of keratinocyte ICAM-1 expression to different T-lymphocyte subsets it was observed that strong or very strong (scores 8–11) keratinocyte ICAM-1 expression, either in DLE or in PLE lesions, associated statistically significantly more often with adjacent intra- or subepidermal CD45RO⁺ cell infiltrates than with

CD45RA⁺ or CD31⁺ cell infiltrates ($p=0.003$ and 0.0004 , respectively, Fig. 1).

DISCUSSION

We examined the dermal and epidermal infiltration pattern of naive and memory T-cells in UVA- and UVB-induced and spontaneous DLE and PLE lesions to find eventual differences between the 2 diseases. We also compared the findings with those obtained from the UVR-provoked healthy skin of control persons. As our main intention was to evaluate the ongoing

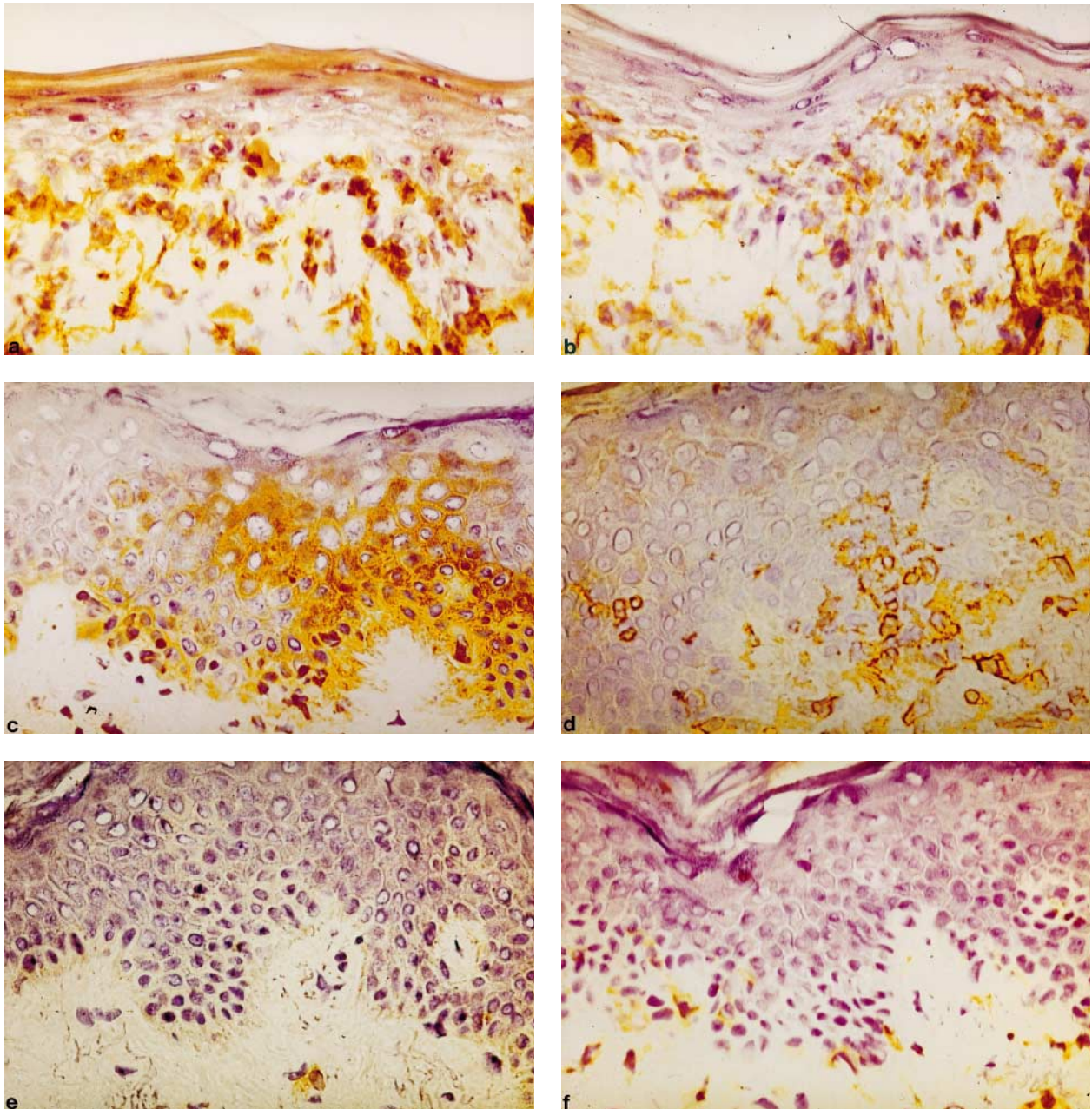


Fig. 1. Immunohistochemical staining of a 21-day-old UVB-provoked DLE lesion, showing intra- and subepidermal cell infiltrates of (a) CD45RA⁺ cells and (b) CD31⁺ cells in the corresponding areas. (c–f) A positive association between ICAM-1 expression and CD45RO⁺ cells, but not between ICAM-1 expression and CD45RA⁺ cells or CD31⁺ cells is shown (8-day-old lesion): (c) intense ICAM-1 expression in the keratinocytes, (d) prominent infiltration of CD45RO⁺ cells in the same area, (e) some scattered cells but no major infiltrates of CD45RA⁺ cells or (f) inflammatory CD31⁺ cells in the corresponding area. Note that several CD31⁺ cells seen in the upper dermis are endothelial cells. (Counterstain haematoxylin, magnification $\times 400$).

immunological process necessary to maintain the skin lesion and not the initial UVR-induced events, the serial biopsies were taken several days or weeks after UVR provocation.

It was typical only for DLE lesions that CD45RA⁺ cells were the prevailing cell population among inflammatory cell infiltrations. The phenomenon that in some DLE lesions the proportion of both CD45RA⁺ and CD45RO⁺ cells was over 50%, refers to the dual positivity of these 2 antigens. This obviously means an interchanging phase between CD45RA⁺ and CD45RO⁺ cells, which has been shown to occur (11). The observation of CD45RA⁺ cell dominance in DLE lesions together with our finding that intra- or subepidermal CD45RA⁺ cell infiltrates were more common in DLE than in PLE lesions suggests a role for CD45RA⁺ cells (regarded as suppressor inducer cells) in the pathogenesis of keratinocyte damage in DLE. Interestingly, the activity of SLE has been reported to associate positively with the number of circulating CD45RA⁺ cells, but not with CD45RO⁺ cells (regarded as helper inducer cells) (18), which also refers to pathogenetic role of CD45RA⁺ cells in the process of LE. A contradictory finding with the present study was reported previously (19). According to this study only minor amounts of naive T-cells were found in DLE skin lesions. Compared with the present study, however, monoclonal antibodies of different source were used. Furthermore, the number of DLE lesions examined in the previous study was only 4 and the age of the lesions was not stated. As PLE patients were not biopsied later than 8 days after the provocation, we cannot totally exclude the possibility that biopsies taken at a later time-point from PLE lesions would have revealed more CD45RA⁺ infiltrations. It is not probable, however, that the clinically entirely resolved reaction sites would have contained considerable amounts of pathogenetically important inflammatory cells.

Our finding of CD45RO⁺ cell dominance among the inflammatory cell infiltrates elicited by UVR provocation in healthy control skin agrees with the recent report of selective influx of memory CD4⁺ T-cells into the human healthy skin upon UVR irradiation (20). As CD45RO⁺ dominance was found in both DLE and PLE skin lesions (spontaneous and photoprovoacted) and, also, in UVR-provoked non-lesional skin of both disorders, influx of CD45RO⁺ cells does not discriminate between DLE and PLE, and is in keeping with earlier reports of preferentially CD45RO⁺ cells in several inflammatory dermatoses (19, 21).

CD31 antigen has been shown to be expressed on such T-cells that mostly display the CD45RA⁺ phenotype (22) and on those CD45RO⁺ cells that are at an intermediate state of maturation (12). The infiltration kinetics of CD31⁺ cells followed rather that of CD45RA⁺ than CD45RO⁺ cells in the present study.

Concurrent with the previous studies, the endothelial expression of E-selectin/P-selectin and ICAM-1 were upregulated with UV-provocation in healthy control persons, whereas the expression of CD31⁺ did not change due to UV irradiation (23, 24). Between the 2 diseases examined, there were no major differences in the endothelial expression of any of the adhesion molecule studied. This suggests that the mechanism of adhesion and transmigration of the T-lymphocytes through the dermal endothelial cells does not differ in the skin lesions of PLE and DLE.

In several skin disorders, colocalization of ICAM-1-positive

keratinocytes and leukocytic dermal infiltration has been observed (8), whereas in early UVR-induced LE lesions, such an association has not always been found (25). We now show that a strong epidermal ICAM-1 expression associates statistically significantly more often with CD45RO⁺ than with CD45RA⁺ or CD31⁺ cell infiltrations. This finding supports the suggestion of recent *in vitro* studies that naive resting CD4⁺ T-cells may utilize other than ICAM-1-mediated adhesion mechanisms (15, 26). However, our finding of a different pattern of intra- or subepidermal infiltration of CD45RO⁺ cells despite an equally strong expression of epidermal ICAM-1 in DLE compared with PLE lesions remains to be explained.

In conclusion, a dissimilar pattern of naive and memory T-cell invasion in the skin in DLE compared with PLE suggests a different immunopathomechanism in these 2 photoaggravated diseases. Furthermore, our findings suggest that besides CD45RO⁺ cells also CD45RA⁺ cells and CD31⁺ cells, attracted to the target site by other than ICAM-1 adhesion, play a role in the development of DLE skin lesions.

ACKNOWLEDGEMENTS

We thank Dr Marika Häkkinen, Ms Marianne Karlsberg and Ms Marja-Leena Koskinen, University of Tampere, for skilful practical assistance in immunohistological staining. We also thank Heikki Kainulainen, PhD, and Anna-Maija Koivisto, BSc, University of Tampere, for laboratory assistance and help with statistical calculations. The results of spectral measurements and dosimetric calculations of phototesting equipment was kindly supplied by Laura Huurto, PhL, Finnish Centre for Radiation and Nuclear Safety, Helsinki. This study was supported by grants from the Medical Research Fund of Tampere University Hospital and The Finnish Rheumatism Association.

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