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Early Events in Ultraviolet Light-induced Skin Lesions in Lupus Erythematosus: Expression Patterns of Adhesion Molecules ICAM-1, VCAM-1 and E-selectin

FILIPPA NYBERG[1], TAINA HASAN[2], CURT SKOGLUND[3] and EIJA STEPHANSSON[1]

[1]Department of Dermatology, Karolinska Hospital and Institute, Stockholm, Sweden, [2]Department of Dermatology, University of Tampere and Tampere University Hospital, Tampere, Finland and [3]Department of Clinical Immunology, Karolinska Hospital, Stockholm, Sweden

In our previous study, photoprovocation induced lupus erythematosus (LE) and polymorphous light eruption-like lesions in photosensitive LE patients. In this new study we examined the expression of ICAM-1, VCAM-1 and E-selectin, in early lesions in particular. A total of 32 patients with cutaneous LE, 25 with "classic" discoid LE, and 7 with systemic LE, including 3 patients with subacute cutaneous LE, were provoked with UVA and UVB on normal appearing skin. Induced lesions were followed up with serial biopsies. LE-like histopathology was seen within 1 week of provocation in some cases. Adhesion molecule expression was statistically significantly affected by the factors clinical diagnosis and wavelength (UVA or UVB). Strong keratinocyte ICAM-1 expression was found 1 week after provocation in reactions that eventually developed into long-standing ones. It is possible that these early changes reflect an underlying defect in the mechanisms that regulate adhesion molecule expression in LE. ***Key words: photo-provocation; photosensitivity; polymorphous light eruption; DLE; histopathology.***

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Filippa Nyberg, Department of Dermatology, Box 120, Karolinska Hospital, S-171 76 Stockholm, Sweden. E-mail: inverness@beta.telenordia.se.

The role of cellular adhesion molecules (CAMs) in inflammatory and neoplastic conditions has been studied extensively in recent years (1). Intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) are members of the immunoglobulin supergene family and recognize leukocyte ligands of the integrin family: lymphocyte function-associated antigen-1 (LFA-1) and very late activation antigen 4 (VLA-4), respectively. E-selectin is a member of the selectin family, and recognizes the carbohydrate ligand Sialyl-Lewis X. These 3 CAMs are essential for leukocyte migration into tissue and leukocyte-mediated cytotoxicity. Induction and/or up-regulation of CAMs in the skin in autoimmune diseases, e.g. systemic lupus erythematosus (SLE), rheumatoid arthritis and systemic sclerosis, has been reported (2). CAM expression in the skin can be influenced by various factors, including environmental factors, such as ultraviolet (UV) radiation (3–5).

In lupus erythematosus (LE), a multisystem autoimmune disease, the skin is the main target organ after joints (6–8). Specific skin lesions in LE are often classified on clinical and histopathological grounds as either acute cutaneous (ACLE) referring to transient, non-scarring lesions seen in SLE and subacute cutaneous LE (SCLE), or chronic cutaneous LE (CCLE), i.e. the typical scarring lesions characteristic of patients with "classic" discoid LE (DLE). DLE patients are usually without systemic symptoms, but LE cases may also present with skin lesions and then progress rapidly to systemic disease (8, 9).

UV radiation has a well-known role in the pathogenesis of skin lesions in the different subsets of LE, but the pathomechanism is still not clear. It has been reported that systemic manifestations can also be induced by exposure to the sun, and skin lesions have been experimentally reproduced by both UVA and UVB (10–12). Photosensitivity in LE can have different clinical presentations. In a previous study, we found that a history of polymorphous light eruption (PLE) was more than twice as common in LE patients than in the normal population (13). Provocation of LE patients with UV light produced both LE-like and PLE-like lesions in the skin (14). In earlier photoprovocation studies, immunohistochemical and micromorphological examinations have focused on established LE skin lesions, persisting clinically for more than 10 days. Evolving and transient lesions have not been investigated previously.

The purpose of this study was to investigate early events in skin lesions induced by UV radiation in LE patients. In serial biopsies we intended to relate CAM expression to clinical appearance and micromorphology of the lesion, provocation wavelength (UVA or UVB) and to time after photoprovocation.

METHODS

Patients and photoprovocations

Photoprovocations with UVA and UVB were performed with 32 photosensitive LE patients, 25 with DLE and 7 with SLE (including 3 patients with SCLE) (Table I). They were included in a cohort of patients with LE that had been evaluated in detail with questionnaires and person-to-person interviews to make clear what kind of photosensitivity they presented (13). PLE was asked about in particular, defined as a history of papular and/or vesicular pruritic eruption arising within a few days after sun exposure on sun-exposed skin, healing spontaneously within 1 week in otherwise healthy individuals. The natural course of the UV-induced skin lesions was followed up clinically, as described previously (14). Two dermatological departments in Scandinavia: Karolinska Hospital, Stockholm, Sweden and Tampere University Hospital, Tampere, Finland were involved.

The provocations were performed on 3 consecutive days in accordance with a protocol described previously (14). The aim of the provocations was to maintain a slight erythema of the test area for several days. UVA provocations were carried out with the UVASUN 3000 (Mutzhas Co., Munich, Germany), a high-pressure metal halide lamp, main emission spectrum 340–400 nm (Karolinska and Tampere). UVB provocations were carried out with either a Waldman UV 1000 Cabin with UV6 bulbs, main emission spectrum 290–370 nm (Karolinska Hospital), or Philips TL 20 W/12, main emission

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Table I. *Clinical data on photoprovoked patients and controls*

	DLE	SLE	PLE	Control
Number (total/females)	25/22	7/6	6/6	7/4
Age mean (range)	46 (14–77)	54 (35–72)	35 (12–52)	30 (16–41)
LE lesions Localized/disseminated	9/9	2/2	0	
PLE (history)	18	2	6	0
ANA	13	5	0	0
SSA (Ro)/SSB (La)	6	6	0	0

DLE: discoid lupus erythematosus, SLE: systemic LE, PLE: polymorphous light eruption, ANA: antinuclear antibody.

spectrum 280–370 nm (Tampere). Detailed data on UVA, UVB and UVC irradiance from each source have been described earlier (14). The test areas were on previously sun-exposed skin, either 5×8 cm (Karolinska Hospital) or 2×2 cm fields (Tampere) on the upper back. Three PLE patients were provoked on the upper arm, where their usual rash had appeared. There were no statistically significant differences, either in clinical data such as sex, distribution and activity of LE lesions or type of photosensitivity, or in outcome regarding number of induced reactions or strength and persistence of these reactions. The UV-induced reactions were evaluated by 2 of the authors (TH, FN) about 24 h after each irradiation, and thereafter every 4–7 days as long as a pathological lesion persisted. Pathological reactions were defined and graded as "weak" = plain erythema lasting for at least 1 week, "moderate" = erythema with papules lasting longer than 3 days or "strong" = either erythema, papules/plaques and DLE-like scaling or erythema with papules and marked oedema. When a reaction was confirmed as pathological, a 4-mm punch biopsy was taken and immediately snap frozen in liquid nitrogen and stored at -70°C until it was processed for immunohistochemistry. Seven non-sun-sensitive control persons and 6 PLE patients were photoprovoked according to the same protocol as the LE-patients, and UV-provocation sites were biopsied 1–7 days after the last provocation. Eighty biopsy specimens from 29 patients were sectioned in half, and half was fixed in formalin and stained with haematoxylin-eosin and PAS for routine histopathological differential diagnosis, based on earlier defined criteria (15–17). The study was approved by the ethics committees of each hospital, and all patients gave informed consent prior to provocations.

Immunohistochemistry

In all, 166 biopsy specimens, 104 of them serial biopsies from photoprovocation sites and 14 from non-irradiated skin in 32 LE patients, were stained for ICAM-1, VCAM-1 and E-selectin (R & D Systems Europe, Ltd. Abingdon, UK). Ten biopsies from irradiation sites in 6 PLE patients and 14 biopsies from 7 controls were also stained as well as spontaneous LE ($n=9$) and PLE ($n=4$) lesions and non-irradiated skin from controls ($n=11$). Briefly, 5–6 μm thick cryostat sections were fixed in acetone followed by chloroform and blocked with normal horse serum. The sections were then incubated with primary mouse monoclonal antibodies (dilution 1:1000 for all antibodies), followed by biotinylated secondary antibody. After quenching of the endogenous peroxidase with 0.3% H_2O_2 in methanol, the sections were incubated with avidin-biotin peroxidase complex using a commercially available kit, Vectastain Elite ABC (Vector Laboratories, Burlingame, CA, USA) according to the manufacturer's instructions. The reaction was visualized with 3-amino-9-etylcarbazole (AEC) or with diaminobenzidine (DAB), then slides were counterstained with Mayer's haematoxylin and mounted. The immunostained sections were examined in a Leitz Diaplan microscope and microphotographs were taken with a Leica Wild MPS 52 equipment. The slides were first evaluated by 1 of the authors (ES) together with either of 2 others (FN, TH). Then the slides were examined independently and evaluated without knowledge of identity, diagnosis or time-point of the biopsy. A semiquantitative scoring system was used in order to obtain a more objective comparison and to allow statistical analysis. Most of the slides were seen by 1 author (ES) and, in the case of different scoring, a consensus solution was found after discussion. For each time point, staining was graded from the lowest to the highest score as follows:

ICAM-1. "Epidermal": focal basal staining of keratinocytes, linear basal staining, focally throughout the epidermis, linear throughout the epidermis, combination of linear, basal and focally throughout the epidermis.

"Follicular": basal staining or staining of whole follicle.

"Endothelial": weak, moderate or strong staining. On cells in infiltrate: perivascular, diffusely spread, combination of perivascular and diffusely spread, band-like.

The proportion of ICAM-1+ cells in the dermal infiltrates was also graded, from 1–3 for $<25\%$, 25–75% or $>75\%$ of infiltrating cells considered positive.

VCAM-1. "Epidermal": negative, weak, strong or follicular. VCAM-1 staining on endothelial and infiltrating cells, were graded according to the same scale as ICAM-1 (see above).

E-selectin. Negative, partial, staining of whole vessel (weak, moderate, strong or granular). The proportion of E-selectin positive vessels was graded from 1–3 on the horizontal and vertical axis of the specimen, respectively, and association between E-selectin on endothelial cells and presence of inflammatory infiltrate was graded as none, weak or strong.

The scores were recorded in protocol forms together with clinical data and histopathology as well as immunofluorescence (IF) findings (18).

Statistical methods

Kruskal-Wallis non-parametric analysis of variance was used when comparing total scores between diagnostic groups. For comparison between groups with long or short duration, Fisher's exact test (2-tailed), or chi-square test (for more than 2 groups) were used. Analysis of variance with repeated measures (general MANOVA) was calculated for the dependent factors ICAM-1, VCAM-1 and E-Selectin expression (median of maximal scores in each diagnostic group). Two independent factors; diagnosis (4 levels) and UV-irradiation (2 levels) were analysed. p values <0.05 were considered statistically significant.

RESULTS

Both transient and more persistent (duration >2 weeks) reactions were induced by UVB and/or UVA in patients with LE. UVB induced reactions in all patients, while UVA produced only pigmentation in 10 of the patients. The transient reactions (16 patients) were clinically PLE-like or unspecific. PLE diagnosis was further supported histologically in 15 of these reactions.

More persistent reactions were induced in 22 patients, 6/7 SLE and 16/25 DLE patients ($p<0.01$). UVA more commonly induced persistent reactions in SLE patients than UVB (6 vs. 4 patients), while there was no difference in the number or duration of reactions produced by different wavelengths in DLE. Among the persistent reactions, clinically LE-like and histologically confirmed LE lesions were found (14). The earliest finding of histopathological characteristics of LE was found already 3 days after the first provocation with UVB. The reaction was clinically graded as

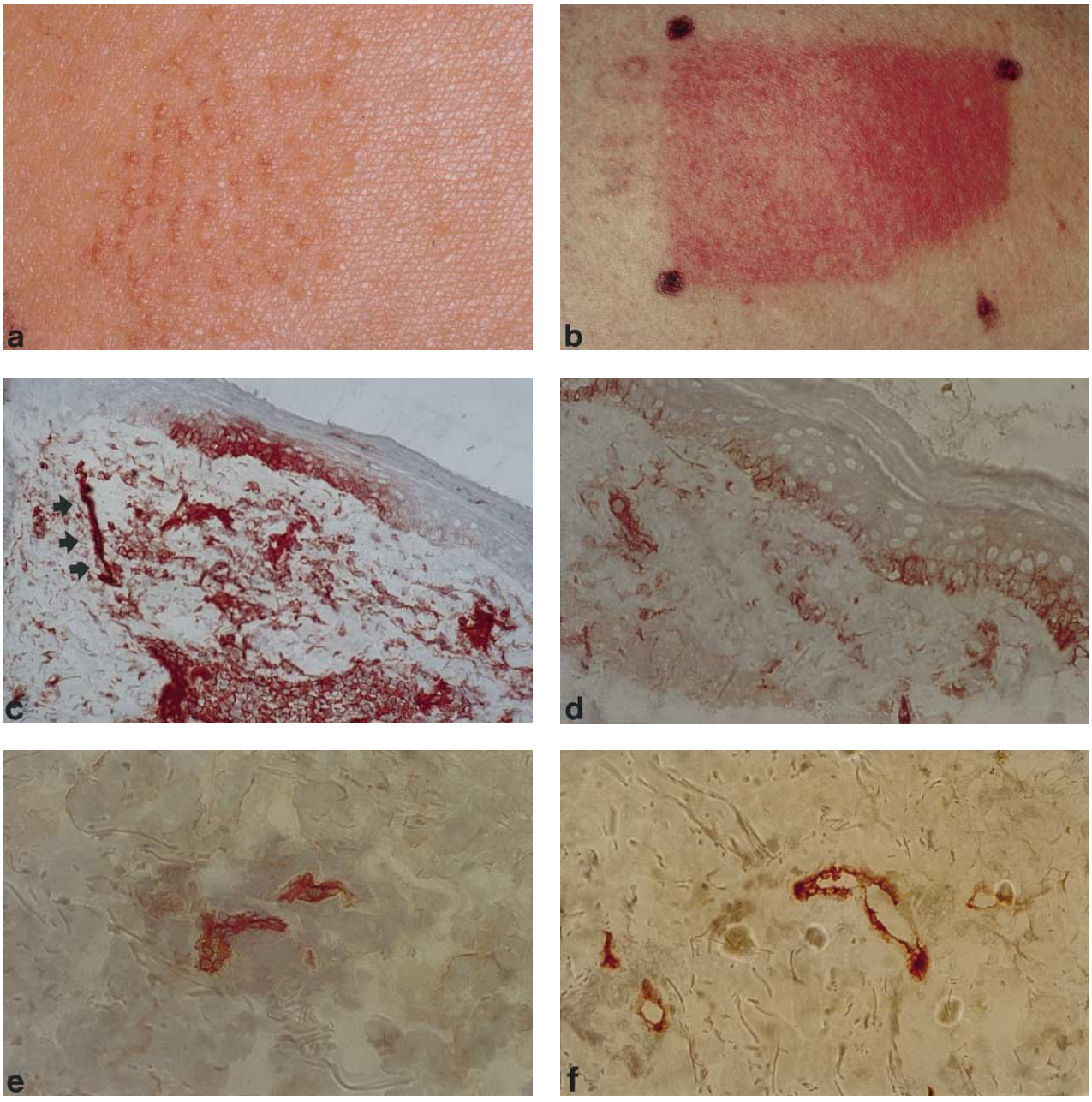

Fig. 1. (*a*) Papular lesion in the provoked area at day 3 after the first provocation with UVA in a patient with DLE and a history of PLE. (*b*) Erythematous, infiltrated plaque in UVB provocation site in an SLE patient. (*c*) ICAM-1 positive keratinocytes overlaying an intensely staining dermal infiltrate as well as endothelial cells (*arrows*). This pattern was seen in PLE patients (× 100). (*d*) Basal expression of ICAM-1 on keratinocytes. Endothelial cells and scattered inflammatory cells in upper dermis express ICAM-1. Early lesion in DLE patient. (× 250). (*e*) E-selectin expression on endothelial cells, all E-selectin + vessels seem to be surrounded by inflammatory infiltrate. Pattern seen in PLE (× 100). (*f*) Marked E-selectin expression in DLE patient after provocation with UVA, presence of vessels also without surrounding infiltrate (× 400).

weak. In serial biopsies, 6/13 with histopathological features of LE were obtained during the first week after irradiation and some of these reactions were clinically unspecific with only persistent erythema and slight infiltration of the skin. Only transient reactions were induced in the PLE patients.

Immunohistochemistry

Statistically significant findings in the evaluation of CAM expression are summarized in Table II. Keratinocytes expressed ICAM-1 in pathological lesions induced by both wavelengths from 3 days after first exposure of the skin. Linear ICAM-1 expression along the basal layer was seen from the earliest biopsies in SLE patients, whereas most induced lesions in DLE patients showed ICAM-1 focally along the basal layer. In SLE patients, the keratinocyte ICAM-1 expression increased with time, while in patients with a diagnosis of DLE it remained stable at a lower level than in SLE. At all time points, keratinocyte ICAM-1 expression was significantly stronger in SLE patients than in DLE and PLE

patients ($p=0.05$). Follicular keratinocyte ICAM-1 expression was prominent and located also suprabasally in many biopsies from patients with LE. In biopsies from induced lesions in PLE patients, ICAM-1 was seen focally throughout the epidermis at day 3, but faded to weak focal basal expression within 7 days of exposure.

Endothelial ICAM-1 expression was up-regulated to moderate or strong expression in lesional skin both in LE and PLE patients and was also up-regulated in non-lesional skin in LE patients, but not in PLE or controls. ICAM-1 was expressed on infiltrating cells with perivascular location as well as on diffusely spread dermal infiltrate in LE patients, with an increasing proportion of ICAM-1 positive cells in infiltrates in lesions persisting for more than 2 weeks.

VCAM-1-positive cells were found in the epidermis in 11/149 (7%) biopsies, 4/11 of these from DLE patients, 4 from SLE, 2 from PLE patients and in 1 control. In 4 biopsies from LE patients, VCAM-1 positive dendritic cells were seen in the epidermis. The strongest VCAM-1 expression on cells in dermal infiltrate, was seen in SLE patients ($p<0.01$). Endothelial VCAM-1 expression was markedly up-regulated in patients compared with controls from day 3 after exposure. Significantly stronger endothelial VCAM-1 expression was seen in SLE than in DLE and PLE, and in lesions induced by UVA compared with UVB. Endothelial cells in clinically uninvolved sun-exposed skin from LE patients expressed VCAM-1, while in healthy controls VCAM-1 endothelial staining was minimal or absent in most cases.

E-Selectin was up-regulated on endothelial cells from day 3 in induced lesions in all patients compared to controls ($p=0.01$). In LE patients, vessels could be seen with strong E-selectin expression without surrounding infiltrate. E-selectin staining was absent or minimal on endothelial cells in controls, including healthy skin in patients.

Clinical diagnosis was found to be the main factor indicating keratinocyte ICAM-1 expression and endothelial VCAM-1 expression, with significantly higher scores in the SLE group for these variables than in DLE and PLE ($p<0.01$). UVA gave significantly stronger endothelial VCAM-1 expression, and more often produced E-Selectin expression without association to infiltrate ($p<0.001$) than UVB.

In biopsies from day 7 after irradiation, persisting lesions induced by UVB showed significantly stronger keratinocyte ICAM-1 expression than transient lesions and persisting lesions induced by UVA showed E-selectin positive vessels without surrounding infiltrate while in transient lesions such vessels were not seen.

Results of some of the slides are seen in Fig. 1.

DISCUSSION

The mechanisms by which UV radiation can induce or exacerbate cutaneous lesions in LE are still not clear, but UV radiation could activate immune receptors, cytokines and cascades of events involving cellular signalling and apoptosis (19).

We have examined serial biopsy specimens from experimentally induced, evolving cutaneous lesions in LE patients. One main outcome is, that underlying diagnosis is the most important factor to influence CAM expression after UV radiation, with the strongest expression of keratinocyte ICAM-1 and endothelial and inflammatory cell VCAM-1 seen in SLE patients.

It has been shown *in vitro* and *in vivo*, that the primary cytokines IL-1 and TNF-α are released from keratinocytes upon UV exposure. TNF-α and IFN-γ, but not IL-1, directly stimulate ICAM-1 expression on cultured keratinocytes (19). Keratinocyte ICAM-1 expression has been shown *in vitro* to be biphasic with an initial down-regulation and then up-regulation 12–24 h after UV stimulation. E-selectin and VCAM-1 are minimally expressed by resting endothelial cells in the skin, but are induced by cytokines, such as TNF-α, IL-1 and IFN-γ (3). Recently, UVA and UVB were shown to induce E-selectin in healthy controls, but only UVA induced E-selectin on cultured endothelial cells (20).

We found that suprabasal ICAM-1 expression in lesional epidermis, was a consistent finding in SLE patients and in

Table II. *Adhesion molecule expression in experimentally UV-induced[a] reactions in LE, PLE and controls. Summary of relevant findings, median scores, etc. explained in Methods.*

	ICAM-1 (CD 54)	VCAM-1 (CD 106)	E-Selectin (CD62E/62P)
DLE $n=25$	K: Focal basal, stable with time**	Epidermis: presence of VCAM-1+ lymphocytes and dendritic cells E: Up-regulated**	Up-regulated**
SLE $n=7$	K: Linear, increasing with time to bandlike, suprabasal***	As in DLE plus I: Strong expression**	As in DLE
PLE $n=6$	K: Early focal, basal, fading within 1 week**	E: No or minimal	Strong expression, in association with dermal infiltrate
Non-lesional skin in LE $n=14$	K: Negative E: Up-regulated**	E: Up-regulated**	No or minimal expression
Controls $n=7$	K: Negative E: Weak, I: Scattered	No or minimal expression	No or minimal expression

[a] Data on biopsies from UVA- and UVB-induced lesions were combined in each diagnostic group, since statistical analysis showed that clinical diagnosis had more influence on adhesion molecule expression than wavelength. Data on significant differences between outcome of UVA vs. UVB provocations are given in the Results.

ICAM: intercellular adhesion molecule, VCAM: vascular adhesion molecule, DLE: discoid LE, SLE: systemic LE, PLE: polymorphous light eruption, K: keratinocyte, I: inflammatory cells (lymphocytes mostly), E: endothelial.

** $p<0.01$ and *** $p<0.001$ for statistically significant difference in median score compared with controls.

early biopsies from persisting and LE-like lesions in all LE patients. Different patterns of CAM expression have been shown, e.g. in UV-induced erythema and in the PPD reaction (21), and a pattern suggestive for delayed hypersensitivity has been reported in PLE (22, 23). In 3 dermatoses classified as interface dermatitis (Lichen Planus, Erythema Multiforme and SCLE), ICAM-1 expression patterns were different (24). In SCLE, keratinocytes express ICAM-1 in the whole epidermis according to Norris and co-workers as well as others (25, 26). In a study on DLE and SCLE patients, both focal, basal and diffuse epidermal ICAM-1 staining was reported, and endothelial ICAM-1 staining was more common in SCLE (27). In a previous study, we found different patterns of CAM expression in different subtypes of LE and in PLE (28). Basal keratinocyte ICAM-1 expression has been thought to be the result of TNF-α and/or IFN-γ released from lymphocytes in underlying infiltrate, whereas the pattern with suprabasal ICAM-1 expression could be triggered by external influence, such as UV radiation (5, 25).

Endothelial cells showed increased expression of all 3 CAMs, both in lesional and healthy, sun-exposed skin in LE patients compared with controls in our study. The same finding has been reported from non-sun-exposed skin in SLE patients, with correlation with disease activity and glucocorticoid treatment (29). Activation of endothelial cells is probably an early step in the cascade of events leading to different types of inflammation in the skin, since activated endothelial cells express CAMs that are necessary for the "skin homing" T lymphocytes to migrate and accumulate at the site (19).

Early skin lesions in different subtypes of LE can be difficult to classify, both clinically and micromorphologically, or to differentiate from PLE (30–32). We found strong CAM expression in early biopsies from UV-induced reactions that developed into long-standing ones. The characteristic micromorphological features of at least DLE are generally regarded to develop slowly. It is therefore worth pointing out, that in the 19 LE patients for whom sequential biopsies from experimentally induced lesions were available, both "acute" and "chronic" LE micromorphological changes could be seen as early as within 1 week after the first UV provocation. In earlier studies on experimentally UV-induced lesions, biopsies were taken from clinically confirmed LE lesions (10). In 1 of our patients with SLE, clinical changes were unimpressive but biopsy revealed LE changes 3 days after provocation.

E-selectin expression in lesional skin was different in LE patients than in PLE patients, with presence of E-selectin-positive vessels without surrounding infiltrate in LE patients, especially in reactions induced by UVA. This pattern of E-selectin expression, together with reports of elevated levels of VCAM-1 in serum from SLE patients (33) and our recent finding of elevated E-selectin in serum from patients with cutaneous LE and active, widespread lesions (34), could indicate a more direct role of endothelial cells in LE than previously assumed. The pathogenesis of UV-induced LE lesions remains speculative (5, 35). Recently, UV-induced keratinocyte apoptosis was proposed as a mechanism for exposure of hidden epidermal antigens to the immune system (36), but the role of UV irradiation reaching to the dermis has not been evaluated.

In summary we have shown obvious differences in the CAM expression in experimentally UV-induced reactions in LE patients vs. PLE patients and healthy controls already in the first week after irradiation. Also, fully developed histopathological LE features were seen in early biopsies. Our findings point to a dysregulation of CAMs, both on the epidermal and on the endothelial level as an important factor in the pathogenesis of UV-induced cutaneous LE lesions.

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