Adhesion Molecule Expression in Polymorphic Light Eruption

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Endothelial leukocyte adhesion molecule-1 (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) are cytokine-regulated cell-surface leukocyte adhesion molecules. We have investigated the in vivo kinetics and pattern of expression of these adhesion molecules in relation to tissue accumulation of leukocytes in the photodermatosis, polymorphic light eruption (PMLE), which is characterized by dense perivascular leukocytic infiltration. Immunohistology was performed on biopsies taken at varying time points from PMLE lesions induced in 11 subjects by suberythemal solar simulated irradiation. Vascular endothelial ELAM-1 expression was first observed at 5 h, maximal at 24 to 72 h, and remained elevated at 6 d. VCAM-1, minimally expressed in control skin, was induced above background levels on endothelium and some perivascular cells after 24 h and maintained at 6 d. Endothelial cell ICAM-1 expression was increased above control levels at 72 h and 6 d. Keratinocyte ICAM-1 expression, most marked overlying areas of dermal leukocytic infiltration, began at 5 h and was strong at 72 h and 6 d. In addition to lymphocytes, significant numbers of neutrophils but not eosinophils were detected in the dermal leukocytic infiltrate that appeared at 5 h and persisted at 6 d. The pattern of adhesion molecule expression that we have observed is similar to that seen in normal skin during a delayed hypersensitivity reaction. These observations support an immunologic basis for PMLE. *J Invest Dermatol 99:504–508, 1992*

Epstein in 1942 [1] first proposed that polymorphic light eruption (PMLE), a common photodermatosis, might represent type IV hypersensitivity to a sunlight-induced cutaneous antigen. Not only is there a delay in onset of PMLE lesions of up to 2 d after sun exposure, but the histologic appearance of lesions is characterized by dense perivascular dermal lymphocytic infiltration in association with increased macrophage and Langerhans cell numbers, resembling allergic contact dermatitis [2].

Dermal infiltration by leukocytes begins with adhesion to endothelial cells (EC), followed by adherence to other cells and extracellular matrix, which thereby influence the distribution, function, and persistence of leukocytes in the skin. An important function of cytokines may be to control such leukocyte traffic through the regulation of inducible cell-surface adhesion molecules such as endothelial leukocyte adhesion molecule-1 (ELAM-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1).

ELAM-1, first characterized using cultured umbilical vein EC, acts as an adhesion receptor for neutrophils, and possibly eosinophils and monocytes, on the surface of cytokine-stimulated cultured EC [3–5]. ELAM-1 is minimally expressed by resting EC, but can be induced by interleukin-1 (IL-1), tumor necrosis factor-α (TNFα), and lymphotoxin, but not by interferon-gamma (IFN-G) [6,7]. Observations of ELAM-1 expression in situ in human skin have shown transient increases in expression in UVB erythema [8] and more persistent elevation in type IV hypersensitivity responses such as following intradermal injection of streptokinase-streptodornase or tuberculin-purified protein derivative (PPD) [8,9] or in allergic contact dermatitis [10].

Unlike ELAM-1, ICAM-1 is expressed by a wide variety of cells. ICAM-1 is constitutively expressed on EC and is also found on activated keratinocytes (KC), lymphocytes, and macrophages [11–14]. The degree to which individual cytokines increase ICAM-1 expression depends upon the cell type studied: IL-1 is a strong stimulus for EC but has minimal activity on KC; TNFα behaves like IL-1 with the exception that it is a stronger stimulus for KC; and IFN-G is a relatively weak stimulus for EC but appears to be the major stimulus for KC [11–14]. The leukocyte receptor for ICAM-1 is the β2 integrin lymphocyte function–associated antigen-1 (LFA-1) (CD11a/CD18), a heterodimeric glycoprotein receptor expressed by all leukocytes [15]. Thus, ICAM-1 expression by EC and other resident cells could be expected to influence the entry into and migration within skin of most leukocytes.

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Abbreviations:
EC: endothelial cell
ELAM-1: endothelial leukocyte adhesion molecule-1
ICAM-1: intercellular adhesion molecule-1
IL-1: interleukin-1
IFN-G: interferon-gamma
KC: keratinocyte
LFA-1: lymphocyte function–associated antigen-1
MED: minimal erythema dose
PAP: peroxidase anti-peroxidase
PMLE: polymorphic light eruption
PPD: purified protein derivative
TNF: tumor necrosis factor
UVB: ultraviolet B
VCAM-1: vascular cell adhesion molecule-1

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Table I. Time Course for Adhesion Molecule Expression and Leukocyte Infiltration in Induced Lesions of PMLE[a]

Time	ELAM-1	ICAM-1 EC	ICAM-1 KC	VCAM-1 EC	Neutrophils	Eosinophils	Monocyte/ Macrophages	T Cells	LFA-1+ Cells
Control	+	++	−	±	−	−	+	+	+
1 h	+	++	−	±	−	−	+	+	+
5 h	++/+++	++	+/++	+	++	+	+++	++	++
24 h	+++/++++	+++	+/++	+/++	++	+	++++	++++	++++
72 h	+++/++++	+++/++++	++/+++	++/+++	++	+	++++	++++	++++
6 d	++/+++	+++/++++	++/+++	++	++	+	++++	++++	++++

[a] Grading is as follows. i) Adhesion molecule expression: −, absent; +, weak; ++, moderate; +++, strong; ++++, very strong. ii) Leukocyte infiltration (positively staining cell bodies per upper dermal HPF): −, none; +, 1–5; ++, 6–10; +++, 11–20; ++++, >20.

VCAM-1, less thoroughly characterized than ELAM-1 and ICAM-1, is minimally expressed on cultured EC and is induced by IL-1 or TNF [16,17]. The β1 integrin VLA-4 (CD49d/CD29) found on lymphocytes and monocytes represents the leukocyte receptor for VCAM-1 [18], and in vitro experiments indicate that VCAM-1 is a selective adhesion molecule for mononuclear cells [16,18,19]. Induction of VCAM-1 has been demonstrated on vascular EC during the cutaneous response to tuberculin [8,19]. VCAM-1 is not, however, restricted to endothelium and is, for example, also expressed by some perivascular cells and interstitial cells of dendritic morphology during delayed hypersensitivity [8].

In this study we have extended a previous immunohistologic analysis [2] of induced lesions of PMLE in order to examine the expression of the adhesion molecules ELAM-1, ICAM-1, and VCAM-1 and their relationship to the presence of leukocytes during the evolution of this condition.

METHODS

Skin Specimens PMLE was induced in 11 patients (seven female, four male) by exposure of previously affected skin to ≤70% of their minimal erythema dose (MED) of solar simulated radiation (Kratos 2500W, Xenon arc filtered, Model LH/52N/3SS). All subjects developed papules 4–20 h post-irradiation that persisted 5–10 d. Four-millimeter punch biopsies (n = number of patients from whom specimens were obtained at each time point) from exposed skin were obtained at 1 h (n = 1), 5 h (n = 1), 24 h (n = 5), 72 h (n = 4), and 6 d (n = 2) after irradiation. Control biopsies were obtained pre-irradiation and from three normal subjects 5 h and 24 h following irradiation in a similar manner. All specimens were bisected; one half was snap frozen in liquid nitrogen and stored at −70°C, the other half fixed in formalin and paraffin-embedded. Hospital Ethical Committee approval was obtained for a maximum of three biopsies per subject.

Staining of Frozen Sections Five-micrometer cryostat sections were obtained from the unfixed frozen specimens stored in liquid nitrogen and mounted on glass slides. Each slide was air dried for 5 min, fixed in acetone for 10 min, and subsequently stained by the three-layer peroxidase anti-peroxidase immunohistochemical assay [20], with 3′,3′-diamino-benzidine (DAB) as substrate. Primary murine monoclonal antibodies employed were 1.2B6 (ELAM-1), 6.5B5 (ICAM-1), 1.4C3 (VCAM-1) [21,22], EN4 (pan endothelial cell) [23] (Bradshure Biologicals, Loughborough, Leicestershire), Leu-1 (CD3, pan T-cell) (Beckton-Dickinson), NP57 (neutrophil elastase) [24], EBM11 (CD68, pan monocyte-macrophage), MHM24 (CD11a, LFA-1 α chain), and MHM25 (CD18, LFA-1 β chain) (Dako, High Wycombe, Buckinghamshire). The second layer ("bridging") antibody consisted of peroxidase-conjugated rabbit anti-mouse IgG, and was followed by the third layer of mouse peroxidase–anti-peroxidase complex. Controls included omission of primary antibodies and substitution with monoclonal antibodies of similar subclass but of irrelevant specificity. Double staining of sections for ELAM-1 and neutrophil elastase was performed as previously described [25]. Briefly, the procedure was identical for the first antibody 1.2B6, which was visualized with DAB; sections were then incubated with NP57, which was detected with an alkaline-phosphatase system (Dako Ltd). Binding was visualized with fast blue BB salt as chromogen. Sections were then counterstained and mounted as above.

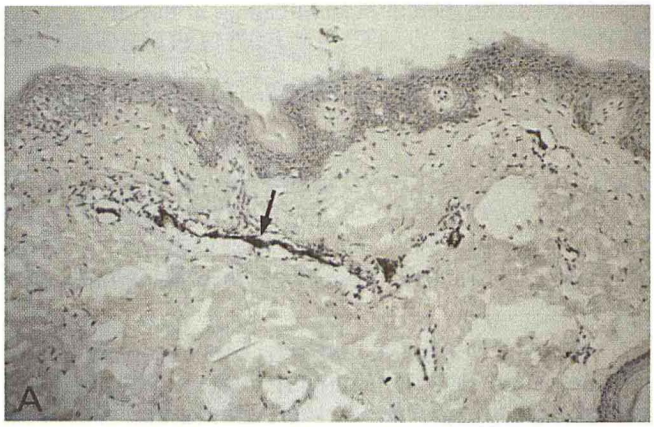
Staining of Paraffin-Processed Specimens Five-micrometer sections cut from paraffin blocks were de-waxed in xylene, rehydrated with alcohol and water, and digested with trypsin. As described previously [26], sections were washed and placed in 10% normal goat serum (Pel-Freez Biologicals Inc., Rogers, AR) overnight. The next day, one section from each block was incubated with affinity chromatography–purified rabbit anti-human major basic protein (supplied by Dr. Gerald J. Gleich) and, as a control, a serial section was incubated with protein A–purified rabbit IgG for 30 min at 30°C. All sections were treated with 1% chromotrope 2R to block nonspecific fluorescence of eosinophils and were finally stained with fluorescein-isothiocyanate–conjugated goat anti-rabbit IgG. Sections were counterstained with hematoxylin-eosin. Both cell-associated fluorescence (intact eosinophils) and extracellular fluorescence (eosinophil degranulation) were determined on the basis of extent and intensity of staining.

Quantification of Adhesion Molecule Expression and Leukocyte Infiltration Extent and intensity of adhesion molecule expression by different cell types in the biopsies was graded as absent, weak, moderate, strong, or very strong on sections assessed in random order by two observers (PGN and JNWNB). Numbers of monoclonal antibody–reactive cell bodies within dermal infiltrates were estimated by counting over at least five adjacent high-power fields (×400) immediately below the dermo-epidermal junction, and results from different subjects were averaged.

RESULTS

Results are tabulated in Table I and examples shown in Fig 1. EC ELAM-1 expression was first evident by 5 h post-irradiation, was maximal at 24 h and 72 h, and had decreased but was still present by 6 d. ICAM-1 expression by basal KC appeared at 5 h and had become stronger at 72 h and 6 d, when it was most apparent overlying areas of leukocytic infiltration in the dermis. Expression of ICAM-1 by infiltrating leukocytes was proportional to their overall numbers. EC ICAM-1 expression was moderately positive in control and test specimens at early time points, but was more marked at 72 h and 6 d when the lymphocytic infiltration was most intense. Moderate ICAM-1 staining, particularly in later biopsies, was also observed on stromal cells and infiltrating cells in the dermis. VCAM-1 was minimally expressed by EC in control skin but was induced above background levels by 24 h, was maximal at 72 h and had declined at 6 d. VCAM-1 expression was also noted on some perivascular cells from 24 h onwards.

Infiltration by neutrophil elastase-positive cells coincided with the appearance of EC ELAM-1 positivity and maximal numbers were observed at 24 h, persisting to 6 d. Elastase positive cells were scattered in the mid and upper dermis and did not enter the epidermis. Only occasionally intact eosinophils or extracellular deposits of major basic protein were noted from 5 h onwards. Infiltration by EBM11-positive cells was observed from 5 h. The characteristics of lymphocyte and macrophage infiltration have been previously de-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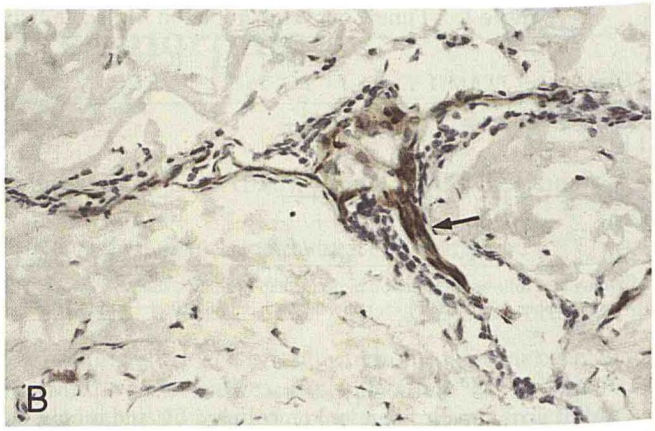
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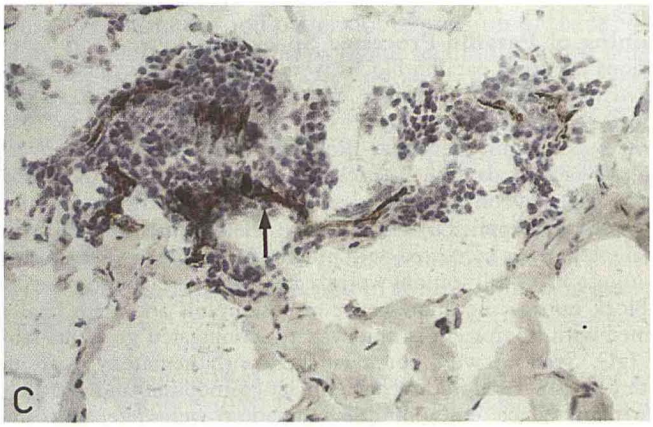
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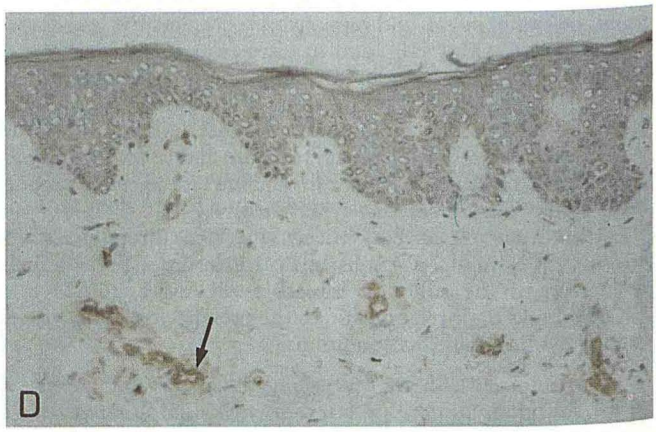
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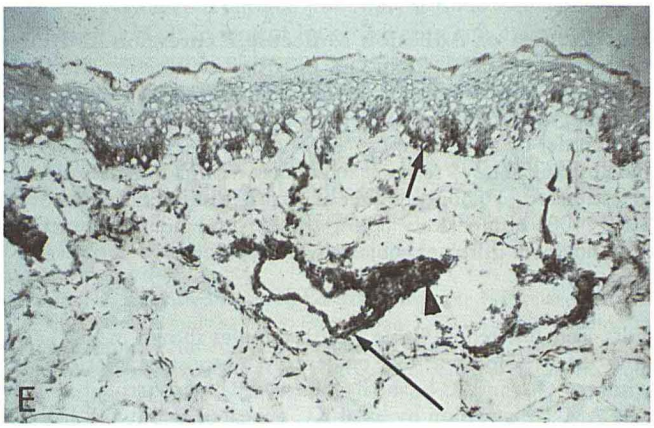
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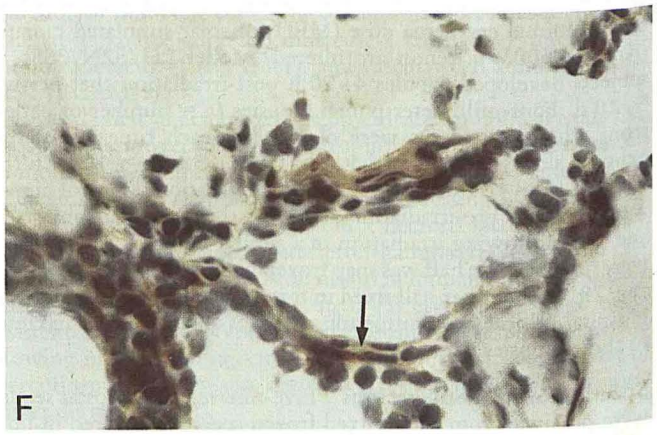
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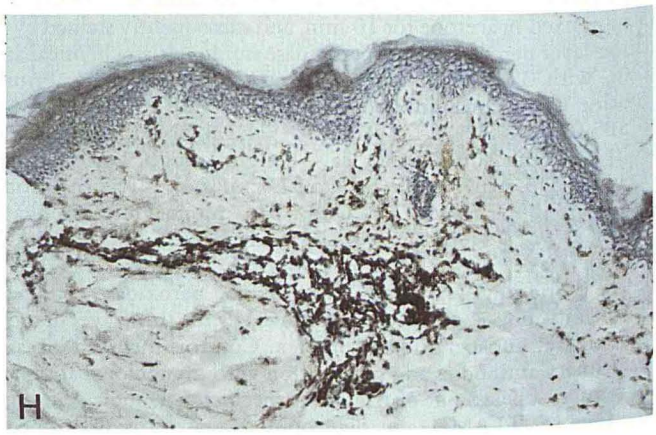
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Figure 1. Immunostaining in PMLE biopsies. ELAM-1 expression (*A*) 5 h (×80), (*B*) 24 h (×125), and (*C*) 72 h (×125) post-irradiation; note restriction of ELAM-1 for vascular endothelium (→). ICAM-1 expression (*D*) pre-irradiation (×80); significant staining is confined to EC (→). ICAM-1 expression (*E*) 72 h post-irradiation (×80); note expression of ICAM-1 by KC (→), EC (⟶), and infiltrating cells (▶). VCAM-1 expression (*F*) 72 h post-irradiation (×250); note strong expression by EC (→). Neutrophil elastase (blue) and ELAM-1 (brown) expression (*G*) 24 h post-irradiation (×250). LFA-1 expression (*H*) 72 h post-irradiation (×80) by infiltrating cells.

scribed in detail [2]. The time course and distribution of infiltrating cells expressing LFA-1 closely resembled that of Leu-1 staining cells.

Biopsies obtained from the irradiated normal controls showed no difference from pre-irradiation sites.

DISCUSSION

A recent immunohistologic study of evolving lesions of PMLE demonstrated predominantly lymphocytic perivascular cellular infiltration associated with increased numbers of dermal macrophages and both dermal and epidermal Langerhans cells within 5 h of UV exposure [2]. In this report, we have further characterized the leukocytic infiltrate in developing lesions of PMLE and correlated this with the expression of the adhesion molecules ELAM-1, ICAM-1, and VCAM-1.

Prolonged ELAM-1 expression in PMLE, still maximally elevated at 72 h and persisting 6 d after irradiation, resembled DTH rather than the more transient expression of ELAM-1 in normal skin irradiated with 2 MED of UV-B [8]. Whether the slight reduction in ELAM-1 expression at 6 d is due to specific down-regulation or merely reflects a general reduction in the inflammatory process is unclear. Because neutrophil tissue infiltration has not been carefully examined previously in PMLE, we studied neutrophils in developing PMLE lesions and demonstrated neutrophil migration into the dermis beginning at 5 h with maximal infiltration occurring from 24 h onwards similar to that observed in DTH [8]. Thus, as in other forms of inflammation, the time course for the appearance of ELAM-1 is paralleled by neutrophil accumulation, further supporting a role for ELAM-1 as an endothelial adhesion receptor for neutrophils in vivo [8,27]. ELAM-1 has also been proposed as an adhesion molecule for eosinophils in vitro [5], but we found only sparse eosinophil infiltration in PMLE suggesting that additional factors are of importance for eosinophil accumulation in vivo.

Strong expression of ICAM-1 by basal KC was observed in established PMLE lesions, particularly overlying areas of intense perivascular dermal leukocytic infiltration, and is likely the result of IFN-γ release by immunologically-activated lymphocytes. Similar KC ICAM-1 expression occurs in DTH reactions such as allergic contact dermatitis [28,29] and the tuberculin response [8] as well as various inflammatory dermatoses characterized by a lymphocyte-rich dermal infiltrate such as atopic dermatitis [30], psoriasis [30], lichen planus [28], and graft-versus-host disease [30]. In contrast, KC ICAM-1 is absent in immunologically non-specific inflammatory reactions such as that to a single exposure of 2 MED UVB in normal skin [8], irritant contact dermatitis [28], and hyperproliferative tape-stripped skin [30].

Recent studies have shown that UV irradiation can inhibit cytokine-induced KC ICAM-1 expression in vitro for up to 24 h [31,32]. Our findings of KC ICAM-1 staining in UV-induced lesions of PMLE from 5 h onwards suggests that any suppressive effect of UV is masked by the triggering of an immunologically mediated tissue response. It has been proposed [31] that induction of KC ICAM-1 48 h following solar-simulated irradiation is due, at least in part, to autocrine release of TNFα [33], and may contribute to the pathogenesis of photosensitive disorders such as subacute cutaneous lupus erythematosus. A similar mechanism may apply in PMLE but further investigations are needed to determine precise mechanisms and which of the possible cytokines are involved.

VCAM-1 is induced on vascular endothelium during the cell-mediated immune response to PPD [8], with maximal expression from 24 h to 1 week, correlating with accumulation of each of the leukocyte types, similar to the pattern we have observed in PMLE. The absence of VCAM-1 induction in the response of normal skin to UVB [8] suggests that VCAM-1 induction on EC in vivo may require the presence of T cells activated in an immune response.

Clinical resolution of induced PMLE lesions preceded return of adhesion molecule expression to baseline levels although there was some evidence of down regulation by 6 d post-irradiation compared with earlier time points. Furthermore, persistent adhesion molecule expression at 6 d was paralleled by lack of resolution of leukocyte infiltration. Thus other factors, such as, perhaps, reduced leukocyte activation, must contribute to clinical disappearance of lesions.

Taken together, these results provide additional understanding of the immunologic basis of PMLE and add further support to the concept that PMLE is not simply an aberrant reaction to UV exposure. Our findings are consistent with the hypothesis that papular PMLE consists of a type IV hypersensitivity reaction to endogenous antigen(s) induced by UV exposure, probably in the dermis, although the nature of the antigen(s) remains obscure.

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