The Perivascular Cell Populations in Human Skin after Topical Application of Leukotriene B_4

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Fifteen timed biopsies of human skin were performed after application of 100 nanograms of leukotriene B_4 in a Finnchamber® for six hours. The number of inflammatory cells were counted per high power perivascular field and compared to three control biopsies. At 24 hours a peak of neutrophiles was observed and subsequently lymphocytes predominated. Eosinophils were never prominent. This pattern of successive cell populations has been described in inflammatory and whealing skin disease. (Received November 25, 1985.)

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Leukotriene B_4 is a potent leukocyte chemotactic compound and after application to human skin it produces epidermal neutrophil abscesses (1). The epidermal abscesses resemble the Munro abscesses of psoriasis, but single and multiple applications to psoriatic skin demonstrated fewer and fewer neutrophils with progressive application (2). The lipoxygenase product 12-HETE also produces epidermal neutrophilia (3).

We decided to review the tissue biopsies available from the first LTB_4 study (1) to trace the perivascular inflammatory cells during the formation and healing of the epidermal abscesses. We found a delayed perivascular (perivenular) neutrophil peak which faded by 48 hours as perivascular lymphocytosis developed.

METHODS

The biopsy slides available from the previous study on application of LTB_4 to normal human skin were reviewed. One hundred ng of LTB_4 had been applied to the small area occluded by a Finnchamber® for 6 hours on the skin of the flexor forearm. Hematoxylin and Eosin and periodic acid Schiff stains were used for each biopsy.

The perivascular areas in the subpapillary zone (perivenular) were isolated in turn by high powered field (×100). Ten consecutive high powered fields were surveyed and all the cells in each field were counted. The two exceptions were at 72 and 96 hours where 8 and 9 fields only could be counted. The number of biopsies at each time period, and the mean and standard deviation of the cell counts of lymphocytes, neutrophils, and eosinophils is summarized in Table I.

RESULTS

The cell counts show a peak of neutrophils in and about the subpapillary venules at the same time as the intraepidermal neutrophil abscesses are at a maximum (Fig. 1). Later, the numbers of neutrophils decrease to low values by 48 hours and the lymphocyte perivascular population rises (Fig. 2). This time sequence is schematically shown in Fig. 3.

COMMENT

The sequence of inflammatory cells in LTB_4 treated skin from neutrophils to lymphocytes is an expected transition in acute to chronic inflammation. However, the delay in appear-

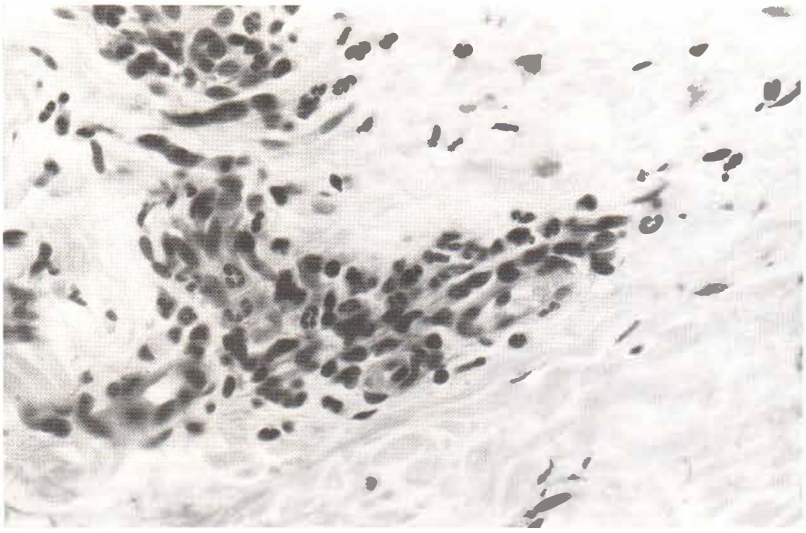

Fig. 1. A skin biopsy 24 hours after LTB_4 application showing vascular and perivascular neutrophils and round cells. H&E, ×460.

ance of the neutrophils is remarkable. Perivascular neutrophils were not observed until 12 hours, and for a potent chemotactic leukocyte chemotactic agent such as leukotriene B_4, a definite delay in absorption of the material must be postulated. An alternative explanation is that LTB_4 produces a biochemical or pharmacologic reaction which over time results in acute inflammation. Dahinden et al. (4) postulated that metabolic products of LTB_4 were active agents and mediators.

We were interested in the marked rise in the perivascular lymphocytes after the acute neutrophilic perivascular inflammation had disappeared. Increased numbers of perivenular lymphocytes were maintained up to 7 days. Since prostaglandins may affect lymphocyte activity, their effect might be an explanation. After such a long period, it might also be appropriate to suggest that the lymphocytes are a response to a chronic vascular injury as in a chronic urticaria. Study of the lymphocyte subsets might be of importance.

Perivascular venular neutrophilia has been observed in dermographism (5, 6) and nicotinate dermographism (7). We have not studied the LTB_4 effect on skin by experimental pressure to demonstrate if the neutrophilia is also accompanied by traumatic vasopermeability, but we might anticipate that both LTB_4 and 12 HETE, which cause vascular

Table I. *Cell populations and LTB_4*

Time	No. of biopsies	Lymphocytes	Neutrophils	Eosinophils
Control	3	13.9±5.5	0	0
6 hours	2	10.9±3.3	0.1±0.3	0
12 hours	2	7.4±3.7	3.5±2.5	0.9±1.0
24 hours	5	9.4±3.8	21.6±7.4	0.9±1.3
48 hours	2	52.7±18.4	5.5±5.4	1.0±1.5
72 hours	2	37.2±12.0	3.5±2.8	0.1±0.3
96 hours	1	57.1±21.5	1.1±1.6	0
168 hours	1	55.1±10.1	0	0

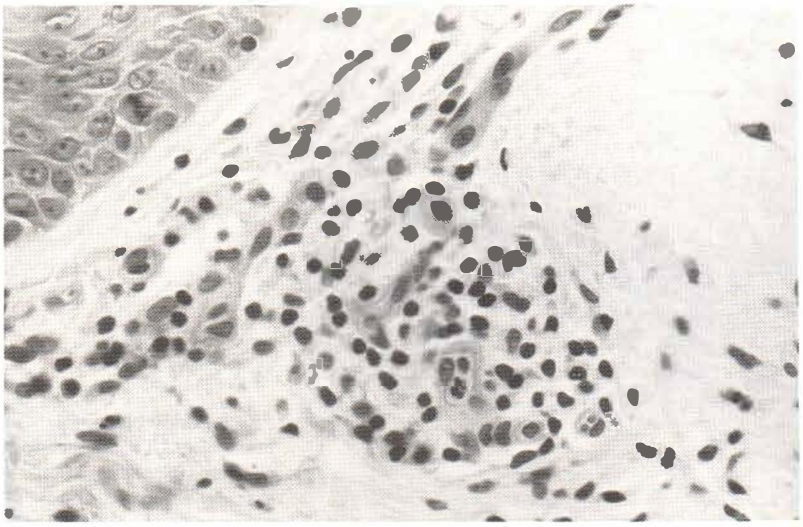

Fig. 2. A skin biopsy at 48 hours showing perivascular round cells (lymphocytes). H&E, ×460.

and epidermal neutrophilia may both condition a dermographic state in human skin. A prospective study is needed to demonstrate if LTB_4 vessel neutrophilia is associated with dermographism.

The transition from neutrophils to lymphocytes has been observed in dermographism (6) and postulated in cold urticaria (8). We have observed this same transition with LTB_4, but delayed by 24 hours. The number of late biopsies makes statistical study impossible and again a prospective study of multiple subjects is needed including both early and late biopsies to document and quantitate the observations of this report. Injection of leukotriene might more closely simulate the early inflammation of whealing states and the reaction might occur much earlier. Another difference from the usual immunologic urticaria is the absence of eosinophils in the studied tissue. Pressure urticaria and some cases of chronic urticaria are marked by significant eosinophilia.

We believe that the neutrophil vascular inflammation is an important feature of the leukotriene B_4 reaction in the skin. Because this reaction occurs in many forms in inflammatory and urticarial disease, it will be important to study these skin diseases for the presence of leukotrienes and lipoxygenase products.

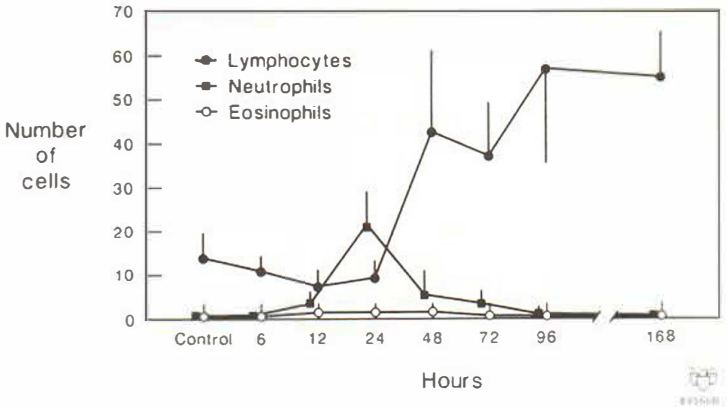

Fig. 3. Schematic representation of mean and standard deviation of cell populations of timed biopsies after application of LTB_4.

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The Epidermal Langerhans' Cell Population in Psoriasis during Topical Coal Tar Therapy

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We have studied the effect on the Langerhans' cell (LC) population of topical 3% coal tar therapy. Biopsies were taken from psoriatic plaques and from controls with no skin disease before and after the application of 3% coal tar for one week; LC were identified by immunofluorescence using monoclonal antibody. LC counts expressed per unit epidermal surface length were similar in untreated psoriasis plaques and in normal skin. Differences in the LC population in paired biopsies from both patients and controls showed considerable variation following coal tar treatment but no consistent effect could be demonstrated. (Received January 8, 1986.)

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The Langerhans' cell (LC) is a bone marrow derived dendritic cell found almost exclusively in the epidermis and responsible for antigen presentation. There are conflicting views on the nature of immune involvement in the pathology of psoriasis (1). A marked reduction in the LC population has been reported following PUVA (2) therapy used in the treatment of psoriasis. It is therefore of interest to determine whether other forms of treatment for psoriasis have this effect.

We have compared the LC population in untreated psoriasis plaques with that in normal skin and after initiation of healing with topical coal tar. This treatment produces a