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Quantitation of Cutaneous Langerhans Cells of Sarcoidosis Patients

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Langerhans cells play a role in cell-mediated immune reactions which are often depressed in sarcoidosis. We examined the epidermis of 17 anergic patients with sarcoidosis (Kveim-reactive and/or biopsy-proved) for the number of Langerhans cells in noninvolved skin and in any cutaneous sarcoidal lesions. Skin biopsies of 10 healthy volunteers served as controls. In comparison to controls, the epidermis overlying noninvolved ($p < 0.05$), sarcoidal ($p < 0.0005$), and Kveim-reactive ($p < 0.005$) skin contained significantly fewer detectable Ia and T6 antigen-bearing Langerhans cells. The reductions within noninvolved skin were most pronounced in patients with multisystem disease. Lower epidermal Langerhans cell densities, in comparison to controls, were detected in both prednisone-treated and untreated patients. Epidermis overlying sarcoidal skin of untreated patients contained significantly fewer Ia and T6 antigen-bearing Langerhans cells ($p < 0.05$, $p < 0.0025$, respectively) than epidermis from noninvolved skin. Whether reduced numbers of cutaneous Langerhans cells are due to either a local and/or systemic effect of sarcoidosis, or reflect the anergic state of these patients is unknown.

Sarcoidosis is a systemic disease of unknown etiology in which cell-mediated immunity is often depressed [1]. Reduced delayed type hypersensitivity in these patients can be detected by hyporeactivity to a wide variety of bacterial, fungal, and viral antigens when skin-tested [2]. Whereas 90–95% of healthy controls exhibit a positive intradermal skin test to *Candida albicans* extract, positive reactions occur in only 40–53% of sarcoidosis patients [3,4]. Further evidence of depressed cell-mediated immunity in the patients include reduction in the proliferative response of blood mononuclear cells to antigens and mitogens, and lower absolute numbers of peripheral blood T lymphocytes [5–7]. On the other hand, there is evidence that the depression in cell-mediated immunity is not absolute [8], in that sarcoidal disease does not delay the rejection of skin homografts [9], and increased numbers of "helper" T lymphocytes are localized within sarcoidal granulomas [10].

Although the origin and function of Langerhans cells has been a matter of conjecture and theory ever since their discovery by Paul Langerhans [11], similarities between Langerhans cells and macrophages recently have been reported. These similarities include plasma membrane 5′-adenosine triphosphatase (ATPase) activity [12], ability to migrate [13], Ia-histocompatibility antigens [14,15], Fc receptors [16], C3b receptors [17], nonspecific esterase activity [18], the ability in vitro to transfer antigen in lymphocyte stimulation [19], and bone marrow derivation [20]. The finding that the Langerhans cells of nonsensitized guinea pigs selectively bind certain common contact allergens led Shelley and Juhlin to coin the term "reticuloepithelial system" for these cells, a system which traps and processes external contact allergens. Langerhans cells are immunocompetent cells playing a pivotal role in cell-mediated hypersensitivity reactions and in the pathogenesis of skin disease [21].

Immunofluorescent detection of cells expressing Ia and/or T6 antigenicity has been used to specifically enumerate Langerhans cells within normal epidermis [22,23]. We investigated 17 anergic patients with sarcoidosis to determine (1) whether within the epidermis, the density of Langerhans cells (as detected by Ia and T6 antigenicity) in noninvolved, sarcoidal, and Kveim-reactive skin differs from that within the epidermis of healthy volunteers, and (2) whether demographic and clinical features of these patients can be related to Langerhans cell density.

PATIENTS

Seventeen of 18 consecutive patients in attendance at the Sarcoidosis Clinic of the Mount Sinai Medical Center considered for inclusion in this study qualified, with the 1 pregnant patient being excluded. None of the 17 patients had received immunosuppressive medications other than glucocorticosteroids (6/17) and none had applied topical steroids for at least 6 months. All 17 patients had clinical features of sarcoidosis and histologic evidence of either a noncaseating granulomatous Kveim test (15/16) or a positive tissue biopsy with noncaseating epithelioid granulomas with little or no necrosis (9/10). Other causes of noncaseating granuloma formation were excluded.

Demographic analysis of these patients revealed a population similar to that of a previous study conducted at this clinic (Table I) [24]. Ten healthly females having an average age of 52.8 years (range 36–65) served as control subjects. The Langerhans cell densities of the skin of this control group (see *Results*) were similar to those of 20 other control subjects in another study (submitted for publication) in which no significant race, age, or sex differences in Langerhans cell densities were detected.

Thirty-five percent (6/17) of the sarcoidosis patients were receiving oral prednisone; 1 patient was receiving 60 mg per day and the others 7.5–10 mg per day. Four of the 6 patients were being treated with prednisone for more than 1 year. Five of the 17 sarcoidosis patients (29%) had sarcoidal skin lesions. All 17 patients were found to be anergic to intracutaneously injected Candidin extract.

MATERIALS AND METHODS

Skin Samples

Following receipt of written informed consent, 4-mm punch biopsies were performed under 1% lidocaine local anesthesia. Twenty-four biopsies were obtained from the 17 patients and 10 from the control subjects. Biopsies were taken of "noninvolved skin" (non-sunexposed medical aspect of the right upper arm, n = 14), "sarcoidal skin" (cutaneous sarcoidosis of extremities, n = 5), clinically "Kveim-reactive skin" (flexor of right forearm, n = 5), and control skin (arm, n = 10). Light microscopic examination of clinically noninvolved skin samples failed to reveal any granulomas.

Kveim Test

Kveim antigen was prepared, testing was carried out, and cutaneous reactions histologically analyzed as previously described [1,25].

Immunofluorescent Detection of Epidermal Langerhans Cells

The following antibodies were obtained commercially: monoclonal mouse antihuman T6 antigen IgG_1 (50 mg/ml; Ortho Pharmaceuticals,

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Abbreviations:
FITC: fluorescein isothiocyanate
PBS: phosphate-buffered saline

TABLE I. *Demographics and disease duration of sarcoidosis patients*[a]

Race	
Black	59%
Caucasoid	25%
Hispanic	16%
Sex	
Female	71%
Male	29%
Years of age	
22–49	71%
50–76	29%
Disease duration	
≤ 2 years	53%
> 2 years	47%

[a] Seventeen sarcoidosis patients anergic to Candidin.

Raritan, New Jersey), monoclonal mouse antihuman Ia antigen IgG_{2b} (1 mg/ml; New England Nuclear, Boston, Massachusetts), and goat antimouse IgG IgG fluorescein isothiocyanate (FITC) (F/P = 4.7; Meloy Laboratories, Springfield, Virginia). Phosphate-buffered saline (PBS) was used for all dilutions and washings.

All samples were processed within 3 h following biopsy. Separation of epidermis from dermis was carried out in 2 N NaBr at 37°C for 30 min. Epidermal blisters were removed intact with fine forceps and bisected. Half of each blister was bathed in 50 μl of either monoclonal mouse antihuman Ia IgG_{2b} (1:100 dilution) or antihuman T6 IgG_1 (1:100 dilution) at 37°C for 1 h. Following 3 10-min washings at 20°C, the samples were incubated in 50 μl of rabbit antimouse IgG IgG-FITC (1:20 dilution) at 37°C for 1 h and washed 3 times. The samples were then mounted between 2 glass coverslips with glycerol gelatin and examined with epifluorescence microscopy and the fluorescing dendritic cells enumerated in at least 10 randomly chosen fields by an examiner who was unaware of the source of the specimen. The density of epidermal Langerhans cells is expressed as the mean number ± SEM per 0.1 mm^2.

Statistics

The mean number ± SEM of Langerhans cells within the epidermis of patient and control groups was determined. Comparisons of the mean epidermal Langerhans cell densities of patient and control groups were performed using Student's *t*-test with *p* values less than 0.05 considered to be significant.

RESULTS

Comparison of the Number of Langerhans Cells Within Epidermis Overlying Noninvolved, Sarcoidal, Kveim-Reactive, and Control Skin

The mean numbers of Ia and T6 antigen-bearing Langerhans cells per 0.1 mm^2 within the epidermis overlying noninvolved skin of 17 sarcoidosis patients (14.1 ± 1.8, 31.5 ± 3.4, respectively) were significantly ($p < 0.05$) less than those within control epidermis (18.3 ± 1.1, 39.5 ± 1.3, respectively). As shown in Fig 1, epidermis overlying sarcoidal skin contained significantly fewer Ia (6.7 ± 0.8) and T6 (16.3 ± 3.7) antigen-bearing cells when compared to either control epidermis ($p < 0.025$). Similarly, epidermis overlying Kveim-reactive skin contained fewer Ia (7.4 ± 1.2) and T6 (20.3 ± 9.0) antigen-bearing cells when compared to either control epidermis ($p < 0.0005$, $p < 0.005$, respectively) or to the epidermis overlying noninvolved skin ($p < 0.025$, $p < 0.10$, respectively). Although, in patients with sarcoidal skin the epidermis overlying noninvolved skin contained only 83% (12.1 ± 1.1) of the Ia and 78% (29.0 ± 7.3) of the T6-bearing Langerhans cells present in the epidermis overlying noninvolved skin of sarcoidosis patients without sarcoidal skin lesions, these differences were not significant.

Comparison of the Number of Epidermal Langerhans Cells of Steroid-Treated and Untreated Sarcoidosis Patients

As shown in Table II, the epidermis overlying either noninvolved or sarcoidal skin for both steroid-treated and untreated patients contained significantly fewer Langerhans cells than control epidermis. However, there are no significant differences in the densities of epidermal Langerhans cells of prednisone-treated and untreated patients. Furthermore, among untreated sarcoidosis patients epidermis overlying sarcoidal skin contained fewer Ia and T6 antigen-bearing Langerhans cells ($p < 0.05$, $p < 0.0025$, respectively) than epidermis overlying noninvolved skin.

Comparison of Epidermal Langerhans Cells in Patients with Both Noninvolved and Sarcoidal Skin

Three patients underwent biopsies of both noninvolved and sarcoidal skin. As shown in Table III, the epidermis overlying sarcoidal skin in each case contained fewer Ia and T6 antigen-bearing Langerhans cells than the epidermis overlying their noninvolved skin.

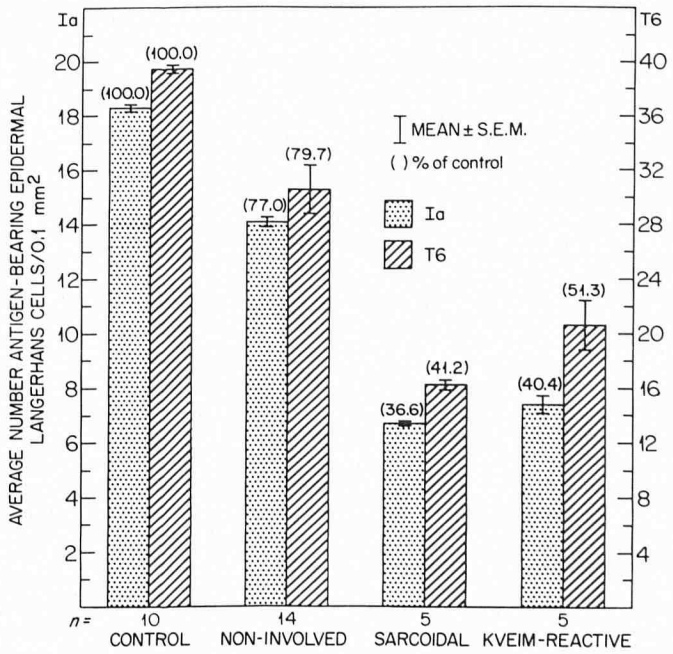

FIG 1. Density of Ia and T6 antigen-bearing Langerhans cells within noninvolved, sarcoidal, Kveim-reactive, and control skin.

TABLE II. *Density of epidermal Langerhans cells in sarcoidosis patients compared to controls*[a]

Subjects/Source of epidermis	Epidermal Langerhans cells/0.1 mm^2 (SD)[b]			
	Ia positive		T6 positive	
	Untreated[c]	Steroid treated[d]	Untreated	Steroid treated
Sarcoid patients/ Noninvolved skin	12.7 (1.8)[e] $p < 0.01$ n = 8	11.3 (1.4) $p < 0.0005$ n = 6	29.5 (2.8) $p < 0.0025$ n = 8	29.7 (3.9) $p < 0.01$ n = 6
Sarcoid patients/ Sarcoidal skin	5.6 (0.8) $p < 0.0005$ n = 3	8.3 (0.4) $p < 0.0025$ n = 2	10.8 (0.0) $p < 0.0005$ n = 3	19.0 (9.1) $p < 0.0005$ n = 2
Healthy controls/ Normal skin	18.3 (1.1) n = 10		39.5 (1.3) n = 10	

[a] Four-millimeter skin biopsies were obtained from 17 sarcoidosis patients and 10 healthy controls.

[b] Epidermal sheets separated from dermis by 2 N NaBr were incubated in monoclonal mouse antihuman Ia or T6 IgG followed by rabbit antimouse IgG IgG-FITC. Ia and T6 antigen-bearing cells were enumerated under epifluorescence microscopy.

[c] Patients not having received immunosuppressive therapy within 2 years.

[d] Patients presently receiving oral prednisone (7.5–60 mg) for at least 3 months.

[e] *p* values refer to *t*-test comparisons of Langerhans cell densities in healthy controls (n = 10) and in the indicated subgroups of sarcoidosis patients.

TABLE III. *Comparison of number of epidermal Langerhans cells within sarcoidal and noninvolved skin of the same patient*[a]

Patient	Epidermal Langerhans cells/0.1 mm² (SD)[b]			
	Ia positive		T6 positive	
	Noninvolved skin	Sarcoidal skin	Noninvolved skin	Sarcoidal skin
1	9.9 (0.9)	4.6 (0.6)	15.0 (1.5)	10.7 (0.9)
2	13.9 (1.4)	8.8 (1.1)	39.2 (2.0)	28.1 (1.0)
3	12.7 (0.5)	7.9 (0.8)	32.8 (0.5)	9.9 (0.7)

[a] Four-millimeter punch biopsies of both noninvolved and sarcoidal skin were obtained from 3 sarcoidosis patients.

[b] Epidermal sheets separated from dermis by 2 N NaBr were incubated in monoclonal mouse antihuman Ia or T6 IgG followed by rabbit antimouse IgG IgG-FITC. Ia and T6 antigen-bearing cells were enumerated under epifluorescence microscopy.

Epidermal Langerhans Cell Morphology

We did not detect any consistent differences in either the dendritic nature or fluorescent staining intensity of either Ia- or T6-bearing Langerhans cells within epidermis overlying noninvolved, sarcoidal, Kveim-reactive, or control skin.

Correlation of Demographic and Clinical Characteristics with the Number of Epidermal Langerhans Cells in Sarcoidosis Patients

The patients with the following clinical characteristics, there were no significant differences in the number of epidermal Langerhans cells in their noninvolved skin: age, $< 50/\geq 50$ years; sex, male/female; race, black/Hispanic/Caucasian; radiographic staging of disease, stage 1/stages 2 and 3; leukocyte count per mm^3, $< 4800/\geq 4800$; elevated lysozyme level, > 13 $\mu g/ < 13$ μg; elevated erythrocyte sedimentation rate per h, $>$ 20 mm/$<$ 20 mm; and elevated angiotensin converting enzyme per nmol min^{-1}, $> 30/\leq 30$. However, patients with recent onset of sarcoidosis ($\leq$ 2 years, "acute-subacute") tended ($p < 0.15$) to have more Ia-bearing Langerhans cells in the epidermis of their noninvolved skin (17.9 ± 4.2) than patients with "chronic" ($>$ 2 years) disease (12.0 ± 2.0). Patients with biopsy-proved involvement of at least one organ system, other than lymph nodes, in addition to lung had significantly fewer Ia-bearing Langerhans cells ($p < 0.05$) in the epidermis of their noninvolved skin (10.5 ± 1.4) than patients with only lung involvement (16.8 ± 2.6) with or without lymph node involvement.

DISCUSSION

The epidermis of patients with psoriasis [26], hyperkeratotic verrucae [27], and contact dermatitis [28,29] has been reported to contain fewer Langerhans cells than present in control skin. In this study, we have found the density of epidermal Langerhans cells within the skin of sarcoidosis patients to be significantly lower than within the skin of healthy volunteers. The reasons for the observed reductions are unclear. It is possible that the fewer numbers of Langerhans cells in these anergic patients reflect a systemic reduction in cell-mediated immunity, which has been suggested to occur in these patients [1,2,9,30]. Langerhans cells play a pivotal role in antigen presentation in contact sensitization, which has been reported to be reduced in patients with sarcoidosis [31].

The lower densities of epidermal Langerhans cells appear to parallel both the duration and extent of systemic sarcoidal involvement. Furthermore, the concept of systemic reductions in Langerhans cells is consistent with the recent finding of no Langerhans cells within alveolar epithelium of 41 sarcoidosis patients, while their presence was detected in normal and fibrotic lungs [32]. Local reductions in the number of epidermal Langerhans cells have been reported in other diseases [26–29] and after exposure to certain agents (33–35). In addition to a general reduction in epidermal Langerhans cells as compared to control skin, our finding of even lower densities of Langerhans cells within epidermis overlying sarcoidal and Kveim-reactive skin than within that overlying noninvolved skin points to more localized reductions in areas of active disease. It is unknown whether these changes are due to the simple obstruction [36] to Langerhans cell migration to the epidermis or to the recruitment of Langerhans cells within dermal infiltrates [37].

Systemic or epicutaneous exposure to glucocorticosteroids has been reported to induce dose-dependent reductions in the density of epidermal Langerhans cells [38–42]. Densities of epidermal Langerhans cells were observed in both steroid-treated and untreated sarcoidosis patients to be less than in controls. Yet, parallel reductions were found in both the steroid-treated and untreated groups of patients and no significant differences were noted between the groups. These findings suggest that the lowered densities of Langerhans cells in these patients were not secondary to a steroid effect. The most probable explanation for the lack of a more pronounced reduction of Langerhans cells in the steroid-treated group is that 5 of these 6 patients were receiving low systemic doses of prednisone (7.5–10 mg per day). Interestingly, the noninvolved skin of the 1 patient receiving 60 mg prednisone daily, had the lowest density (4.2/0.1 mm^2) of Ia-bearing epidermal Langerhans cells of all patients tested.

It has been our experience that the immunofluorescent assay for Langerhans cell Ia expression detects 55–60% of the number of Langerhans cells determined by immunofluorescent detection of human T6 antigen [41,42]. One could speculate that these assays differ in their ability to detect 2 different subpopulations of Langerhans cells, indeterminate Langerhans cells, which have been suggested to be an immature form, and Birbeck granule cell-containing Langerhans cells. T6 antigens are expressed by all Langerhans cells [23] and the possibility exists that the expression of Ia antigens, Fc, and C3b receptors are restricted to differentiated Langerhans cells. Differences in assay sensitivities as the basis for the differences in Langerhans cell detection cannot be ruled out.

In conclusion, we have found the density of epidermal Langerhans cells in sarcoidosis to be decreased; the degree to which this is seen appears to parallel the disease chronicity and multisystem involvement. Whether these abnormal numbers of Langerhans cells are due to a local and/or a systemic effect of sarcoidosis, or reflect the anergic state of these patients is unknown.

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Desmosomal Antigens Are Not Recognized by the Majority of Pemphigus Autoimmune Sera

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Sera from 7 patients with pemphigus vulgaris and both mouse and rabbit antisera against bovine epidermal desmosomes contained antibodies that bound to cell surface components of the spinous layer of bovine epidermis. The antidesmosomal sera showed significant binding to purified desmosomal proteins in an enzyme-linked immunosorbent assay (ELISA). Two of 7 pemphigus sera bound to desmosomal protein-coated microtiter plates at low dilution titers. Two of 6 normal human sera also bound to desmosomal protein-coated microtiter plates

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Abbreviations:
BSA: bovine serum albumin
ELISA: enzyme-linked immunosorbent assay
PBS: phosphate-buffered saline
SDS-PAGE: sodium dodecyl sulfate-polyacrylamide gel electrophoresis