Quantitation of Cutaneous Langerhans' Cells of Sarcoidosis Patients[a]

BRIAN BERMAN,[b,c] JOSHUA L. FOX,[d] AND ALVIN S. TEIRSTEIN[e]

[c]*Department of Dermatology*
School of Medicine
University of California, Davis
Davis, California 95616
and
Veterans Administration Medical Center
Martinez, California 94553

[d]*Department of Dermatology*
New York University School of Medicine
New York, New York 10016

[e]*Department of Pulmonary Medicine*
Mount Sinai School of Medicine
New York, New York 10029

INTRODUCTION

Sarcoidosis is a systemic disease of unknown etiology in which cell-mediated immunity is often depressed.[1] Reduced delayed-type hypersensitivity to a wide variety of bacterial, fungal, and viral antigens is evident in sarcoidosis patients by hyporeactivity in skin tests.[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 sarcoidosis patients includes the reduced proliferative response of blood mononuclear cells to antigens and mitogens, and lower absolute numbers of peripheral blood thymus-derived (T) lymphocytes.[5-7] On the other hand, there is evidence that the depression in cell-mediated immunity is not absolute:[8] 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 have been matters for conjecture and theory ever since the discovery of these cells by Paul Langerhans,[11] similarities between Langerhans' cells and macrophages have recently been reported. Some of the similarities that have been found involve plasma membrane 5'-adenosine

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[b]Address for correspondence: Veterans Administration Medical Center, 150 Muir Road, Martinez, California 94553.

triphosphatase (ATPase) activity,[12] the ability to migrate,[13] I-associated (Ia) histocompatibility antigens,[14,15] crystallizable fragment (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] Langerhans' cells are immunocompetent cells that play a pivotal role in antigen-driven T lymphocyte proliferation, in allogeneic and syngeneic T lymphocyte proliferation, and in the generation of cytotoxic T lymphocytes: Langerhans' cells are also capable of synthesizing immunomodulatory products such as interleukin-1.[21]

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

PATIENTS

Seventeen of 18 patients who were consecutively admitted to the Sarcoidosis Clinic of the Mount Sinai Medical Center and considered for inclusion in this study qualified; the patient that did not qualify was pregnant. None of the 17 patients had received immunosuppressive medications other than glucocorticosteroids, which 6 of the patients had received, and none of the patients had applied topical steroids for at least 6 months. Each of the 17 patients had clinical features of sarcoidosis and histologic evidence of noncaseating epithelioid granulomas: 15 out of 16 patients had a positive Kveim test, and 9 out of 10 patients had tissue biopsies which showed granulomas with little or no necrosis. 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 1).[24] Ten healthy females who had an average age of 52.8 years (range: 36-65 years) served as control subjects. The Langerhans' cell densities in the skin of this control group (see Results) were similar to those of 10 other control subjects in another study in which no significant race, age, or sex differences in Langerhans' cell densities were detected.[25]

Six of the sarcoidosis patients (35%) were receiving oral prednisone; one of these six patients was receiving 60 mg/day, and the other five were receiving 7.5-10 mg/day. Four of these six patients were being treated with prednisone for more than 1 year. Five of the sarcoidosis patients (29%) had sarcoidal skin lesions. All of the sarcoidosis patients were found to be anergic to intracutaneously injected candidin extract.

MATERIALS AND METHODS

Skin Samples

Following receipt of written informed consent, skin biopsies 4 mm in diameter were performed on patients that were 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" from the medial aspect of the right upper arm, that is, of skin that had not been exposed to the sun ($N = 14$); of "sarcoidal skin" from the extremities ($N = 5$); of clinically "Kveim-reactive skin" from the flexor of right forearm ($N = 5$); and of "control skin" from the 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 were histologically analyzed as previously described.[1,26]

TABLE 1. Demographics of and Disease Duration for Sarcoidosis Patients

Clinical Characteristics	Percent of Population[a]
Race	
Black	59
Caucasoid	25
Hispanic	16
Sex	
Female	71
Male	29
Age (years)	
22-49	71
50-76	29
Disease duration (years)	
≤ 2	53
> 2	47

[a]The population comprised 17 sarcoidosis patients who were anergic to candidin extract.

Immunofluorescent Detection of Epidermal Langerhans' Cells

The following antibodies were obtained commercially: monoclonal mouse antihuman T6 antigen IgG1 (50 mg/ml; Ortho Pharmaceuticals, Raritan, New Jersey), monoclonal mouse antihuman DR antigen IgG2b (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 hr after 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 DR IgG2b (1:100 dilution) or antihuman

T6 IgG1 (1:100 dilution) at 37° C for 2 hr. After three 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 hr and washed three times. The samples were then mounted between two glass coverslips with glycerol gelatin and examined with epifluorescence microscopy. The fluorescing dendritic cells were 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 was expressed as the mean number (± SEM) of cells within a 0.05-mm² area.

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, and *p* values of less than .05 were considered significant.

RESULTS

Comparison of the Langerhans' Cell Densities within Epidermis Overlying Noninvolved, Sarcoidal, Kveim-reactive, and Control Skin

The densities of DR-positive and T6-positive Langerhans' cells within the epidermis overlying the noninvolved skin of sarcoidosis patients (14.1 ± 1.8 and 31.5 ± 3.4 cells/0.05 mm², respectively) were significantly ($p < .05$) lower than those within the control epidermis (18.3 ± 1.1 and 39.5 ± 1.3 cells/0.05 mm², respectively); furthermore, as is shown in FIGURE 1, those within the epidermis overlying sarcoidal skin (6.7 ± 0.8 and 16.3 ± 3.7 cells/0.05 mm², respectively) were also significantly ($p < .025$) lower than those within the control epidermis. Similarly, epidermis overlying Kveim-reactive skin contained fewer DR-positive and T6-positive cells (7.4 ± 1.2 and 20.3 ± 9.0 cells/0.05 mm², respectively) than did the control epidermis ($p < .0005$ and $p < .005$, respectively), or, the epidermis overlying noninvolved skin ($p < .025$ and $p < .10$, respectively). In patients with sarcoidal skin, the epidermis overlying noninvolved skin contained only 83% (12.1 ± 1.1 cells/0.05 mm²) of the number of DR-positive cells and 78% (29.0 ± 7.3 cells/0.05 mm²) of the number of T6-positive cells that were present in the epidermis overlying the noninvolved skin of sarcoidosis patients without sarcoidal skin lesions; however, these differences were not significant.

Comparison of the Langerhans' Cell Densities within Epidermis of Steroid-treated and Untreated Sarcoidosis Patients

As is shown in TABLE 2, the epidermis overlying either noninvolved or sarcoidal skin for both steroid-treated and untreated patients contained significantly fewer Lang-

erhans' cells than did the control epidermis. There are no significant differences, however, in the densities of epidermal Langerhans' cells of prednisone-treated and untreated patients. Furthermore, among untreated sarcoidosis patients, the epidermis overlying sarcoidal skin contained fewer DR and T6 antigen-bearing Langerhans' cells ($p < .05$ and $p < .0025$, respectively) than did the epidermis overlying noninvolved skin.

Comparison of Langerhans' Cell Densities within Epidermis Overlying Noninvolved and Sarcoidal Skin

Three patients underwent biopsies of both noninvolved and sarcoidal skin. As is shown in TABLE 3, the epidermis overlying their sarcoidal skin in each case contained fewer DR and T6 antigen-bearing Langerhans' cells than did the epidermis overlying their noninvolved skin.

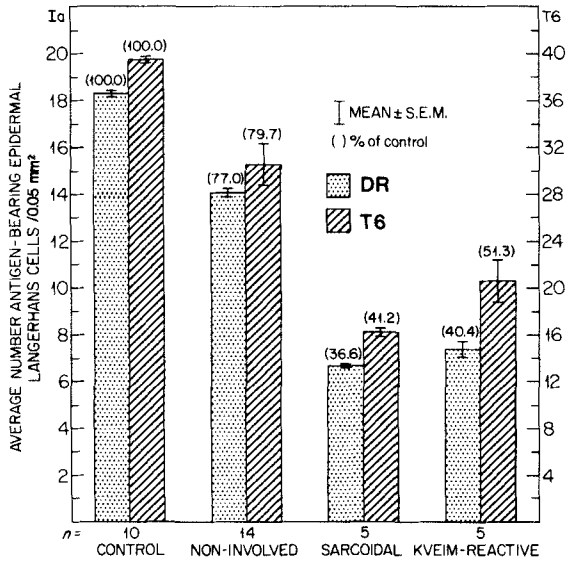

FIGURE 1. The density of DR and T6 antigen-bearing Langerhans' cells within noninvolved, sarcoidal, Kveim-reactive, and control skin.

Epidermal Langerhans' Cell Morphology

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

TABLE 2. Densities of Marked Epidermal Langerhans' Cells in Sarcoidosis Patients Compared to Those in Controls

	Epidermal Langerhans' Cell Density[a] (cells/0.05 mm² ± SD)			
	DR Positive		T6 Positive	
Subjects/Source of Epidermis	Untreated[b]	Sarcoid Treated[c]	Untreated[b]	Sarcoid Treated[c]
Sarcoid patients/Noninvolved skin	12.7 ± 1.8(8) $p < .01$	11.3 ± 1.4(6) $p < .0005$	29.5 ± 2.8(8) $p < .0025$	29.7 ± 3.9(6) $p < .01$
Sarcoid patients/Sarcoidal skin	5.6 ± 0.8(3) $p < .0005$	8.3 ± 0.4(2) $p < .0025$	10.8 ± 0.0(3) $p < .0005$	19.0 ± 9.1(2) $p < .0005$
Healthy controls/Normal skin	18.3 ± 1.1(10)		39.5 ± 1.3(10)	

NOTE: Skin biopsies 4 mm in diameter were obtained from 17 sarcoidosis patients and 10 controls. The number of biopsies taken for each subgroup is indicated in parentheses immediately following the corresponding cell density value. The p values refer to Student's t test comparisons of cell densities in healthy controls to those in sarcoidosis patient subgroups.

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

[b]Patients who had not received immunosuppressive therapy within 2 years.

[c]Patients who had been receiving oral prednisone (7.5-60 mg/day) for at least 3 months.

TABLE 3. Epidermal Langerhans' Cell Densities within Sarcoidal and Noninvolved Skin

	Epidermal Langerhans' Cell Density[a] (cells/0.05 mm² ± SD)			
	DR Positive		T6 Positive	
Patient	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

NOTE: Skin biopsies 4 mm in diameter of both noninvolved and sarcoidal skin were obtained from three sarcoidosis patients.

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

Correlation of Demographic and Clinical Characteristics with Epidermal Langerhans' Cell Densities in Sarcoidosis Patients

No significant differences in Langerhans' cell densities in noninvolved skin depended on any of the following clinical characteristics: whether a patient was < 50 or ≥ 50 years of age; was a male or a female; was a black, a Hispanic, or a Caucasian; was in or beyond stage I of the disease; had < 4800 or ≥ 4800 leukocyte counts/mm^3; had a lysozyme level > 13 or < 13 $\mu g/\mu l$; had an erythrocyte sedimentation rate > 20 or < 20 mm/hr; or had an angiotensin-converting enzyme level > 30 or ≤ 30 nmol/min. Patients in which the onset of sarcoidosis was recent (acute-subacute: ≤ 2 years), however, tended ($p < .15$) to have more DR-bearing Langerhans' cells in the epidermis of their noninvolved skin (17.9 ± 4.2 cells/0.05 mm^2) than did patients with chronic (> 2 years) disease (12.0 ± 2.0 cells/0.05 mm^2). Patients with biopsy-proven involvement, but an involvement not including the lymph nodes, of more than one organ system (that of the lung and some other system) had significantly ($p < .05$) fewer DR-bearing Langerhans' cells in the epidermis of their noninvolved skin (10.5 ± 1.4 cells/0.05 mm^2) than did patients who had only lung involvement (16.8 ± 2.6 cells/0.05 mm^2), whether or not the involvement included the lymph nodes.

DISCUSSION

The epidermis of patients with psoriasis,[27] hyperkeratotic verrucae,[28] and contact dermatitis[29,30] has been reported to contain fewer Langerhans' cells than are 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 that 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, a reduction which has been suggested to occur in these patients.[1,2,9,31] Langerhans' cells play a pivotal role in antigen presentation in contact sensitization, which has been reported to be reduced in patients with sarcoidosis.[32]

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 that Langerhans' cells were present within normal and fibrotic lungs but were not present within the alveolar epithelium of 41 sarcoidosis patients.[33] Local reductions in the number of epidermal Langerhans' cells have been reported in other diseases[27–30] and after exposure to certain agents.[34–36] This study demonstrated a general reduction in density of Langerhans' cells in sarcoidal skin as compared to control skin, and the finding of even lower densities of Langerhans' cells within the epidermis overlying sarcoidal and Kveim-reactive skin than that within the epidermis overlying noninvolved skin suggests there are localized reductions in areas of active disease. It is not known whether these changes are simply due to an obstruction of Langerhans' cell migration to the epidermis[37] or to the recruitment of Langerhans' cells within dermal infiltrates.[38]

Systemic or epicutaneous exposure to glucocorticosteroids has been reported to induce dose-dependent reductions in the density of epidermal Langerhans' cells.[39–43]

The densities of epidermal Langerhans' cells that were observed in steroid-treated and untreated sarcoidosis patients were both less than the density observed in controls; furthermore, parallel reductions were found in both the steroid-treated and untreated groups of patients, and no significant differences were noted between these two 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 five of the six patients in this group were receiving low systemic doses of prednisone (7.5-10 mg/day). Interestingly, the noninvolved skin of the patient that received 60 mg of prednisone daily had the lowest density of DR-bearing epidermal Langerhans' cells (4.2 cells/0.05 mm^2) of any skin type, from any patient, that was tested.

It has been our experience that the immunofluorescent assay for DR-positive Langerhans' cells using Ortho monoclonal antibodies detects 55-60% of the number of Langerhans' cells determined by immunofluorescent detection of human T6 antigen.[42,43] One could speculate that these antigens are present on two different subpopulations of Langerhans' cells: on indeterminate Langerhans' cells, which have been suggested to be an immature form, and on Birbeck granule cell-containing Langerhans' cells. T6 antigens are expressed by all Langerhans' cells,[23] and the possibility exists that the expression of DR 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. Interestingly, not all patients with metastatic carcinomas who are anergic have reduced numbers of Langerhans' cells.[25,44] Although all patients included in that study were anergic, depletion of Langerhans' cells was observed only in patients with metastatic lung cancer and not in patients with metastatic breast carcinomas. Therefore we feel that the reduced number of Langerhans' cells in sarcoidosis patients may reflect the specific disease rather than the anergic state.

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