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Imbalances in T Cell Subpopulations in Lepromatous Leprosy[1]

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The clinico-pathological features of leprosy depend, to a large extent, on the intensity of the cell-mediated immune response to *Mycobacterium leprae* ([6, 7, 21]). It is widely accepted that patients with lepromatous leprosy have a specific deficiency of cell-mediated immunity (CMI) towards *M. leprae*, and a somewhat less important, reversible, generalized depression of CMI. The mechanism of this immune deficiency is not fully understood; among other hypotheses, it has been suggested that active suppressor mechanisms, involving suppressor macrophages or suppressor T cells ([4, 10]), may be involved in the depression of CMI in lepromatous patients. T cells play a central role in the immune responses, especially in CMI. In man as well as in rodents, there are two main subsets of regulatory T cells, T helper cells and T suppressor cells. The physiological interactions between these cell types are important in the regulation of most immune responses.

Hybridoma technology recently provided new tools for the study of T cell subsets in man. Monoclonal antibodies directed at well-defined T cell subsets have been produced. The OKT antibodies prepared by Kung and Goldstein and functionally evaluated by Reinherz and Schlossmann ([17]) represent a set of reagents allowing a precise study of T cell subpopulations.

Three OKT antibodies have been used in this study: OKT 3 recognizes all circulating T cells; OKT 4 recognizes T cells with a helper, or inducer, function ([15]), and OKT 8 recognizes suppressor and cytotoxic T cells ([16]). The ratio OKT 4+ cells/OKT 8+ cells, or the helper/suppressor (H/S) ratio, expresses the balance between the two main subsets of T cells which cooperate in immune responses ([3]).

In a previous report, we have shown that the H/S ratio is normal in tuberculoid patients, and in non-reactional lepromatous patients. This ratio is elevated in lepromatous patients with recent erythema nodosum leprosum (ENL) ([2]). In this paper, we further investigate the imbalances between helper and suppressor T cells in various clinical situations in lepromatous leprosy. Our results show that the H/S ratio is normal only in bacteriologically negative, non-reactional (non-ENL) lepromatous patients. In non-reactional, bacteriologically positive patients, the H/S ratio is diminished. In ENL patients, whatever their bacillary load, the H/S ratio is transiently elevated.

MATERIALS AND METHODS

Patients. Twenty-four lepromatous patients (18 LL, 6 BL), all living in Paris, France, at the time of the investigation, entered this study. They were divided into three groups according to the clinical and bacteriological course of their disease. Group 1 is composed of 6 patients who, at the time of the study, were bacteriologically positive, either untreated (3 patients) or presenting with dapsone (DDS)-resistant lepromatous relapse after long-term sulfone therapy (3 patients); none of them had suffered from ENL recently. One had had ENL five years before. Group 2 is composed of nine efficiently treated, bacteriologically negative patients. None of them had had ENL recently; three had a past history of ENL some years before. Group 3 is composed of nine patients who were admitted because of recent ENL. The beginning of the ENL was less than two months before the study. Most of these patients were febrile, had ENL skin lesions, and had elevated neutrophil counts at the time of the investigation. None of them was receiving

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corticosteroids before, or at the time of the initial evaluation. None of our patients had suffered from Type 1 (reversal) reaction.

A lepromin test (Mitsuda reaction) was performed by injecting intracutaneously 0.1 ml of standardized lepromin (10^7 bacilli/ml), a gift from Dr. Saint-André, Institut Marchoux, Bamako, Mali. It was negative in all of the patients.

The sex, age, geographical origin, classification, duration of disease, therapy, and bacterial load of each of the patients are given in Table 1. Controls were male and female healthy volunteers, members of our department, or blood bank donors, 20 to 60 years old.

Enumeration of T cell subsets with monoclonal antibodies. The indirect immunofluorescence technique for the enumeration of OKT 3+ (pan-T) cells, OKT 4+ (helper/inducer) cells, and OKT 8+ (suppressor/cytotoxic) cells has been previously described in detail ([2]). Briefly, monoclonal antibodies produced by mouse hybridoma and directed against functionally different T cell subsets ([15, 16, 17]) were kindly donated by P. C. Kung and G. Goldstein, Ortho Pharmaceutical Corporation, Raritan, New Jersey, U.S.A.

Peripheral blood mononuclear cells (PBMC) were isolated on a Ficoll-sodium metrizoate gradient (Telebrix, Paris, France). PBMC were suspended in Hanks medium containing 0.2% sodium azide and 5% fetal calf serum and incubated with the appropriate dilution of each monoclonal antibody for 30 min at 4°C. Cells were washed twice and incubated with purified goat anti-mouse IgG antiserum (Miles Laboratories, Inc., Elkhart, Indiana, U.S.A.), labeled with fluorescein isothiocyanate. Cells were left again for 30 min at 4°C, washed twice, and the percentage of fluorescent cells was scored immediately under a fluorescent microscope.

Lymphocyte transformation tests (LTT). Proliferative responses to the mitogens phytohemagglutinin (PHA) (Difco, Detroit, Michigan, U.S.A.), 2 μg/ml; concanavalin A (Con-A) (Pharmacia, Uppsala, Sweden), 50 μg/ml; and pokeweed mitogen (PWM) (Gibco, Grand Island, New York, U.S.A.), 1/20 of the stock solution, were studied by measuring ^{3}H-thymidine incorporation, as previously described ([5]). For each patient, results are expressed as a percentage of the proliferation obtained with the mononuclear cells of a normal subject tested on the same day.

Con-A-induced suppressive activity. This was studied as described by Sakane and Green ([20]). In brief, PBMC were cultured with Con-A for 48 hr and then added to a mixed leukocyte culture (MLC) using autologous PBMC as responder cells. ^{3}H-thymidine incorporation was measured and compared with that obtained in a similar MLC where control cells cultured without Con-A for 48 hr were added.

Skin tests. Each of the following antigens (0.1 ml) was injected intracutaneously in the outer part of the arm: a) tuberculin, 10 units; b) candidin, 10^{-3} of the stock solution (Institut Pasteur, Paris, France), c) Varidase (50 units streptokinase, 12.5 units streptodornase) (Lederle, Madrid, Spain), and d) streptococci (a suspension of 8×10^7 autoclaved bacilli from groups A, B, C, D, N, and O) (Institut Mérieux, Lyon, France). Tests were read after 48 hr and recorded as follows: papular induration of less than 5 mm diameter, 1+; 5 mm to 12 mm, 2+; 12 mm to 20 mm, 3+; more than 20 mm, 4+. The total number of + for the four tests was chosen to express the cutaneous delayed-type hypersensitivity of the patient. Control subjects had a mean DTH score of 9.5 ± 0.4.

DNCB sensitization. Fifty μl of dinitrochlorobenzene (DNCB), 1% in acetone/olive oil was applied to the skin of the back. Two weeks later, 50 μl of 0.1% DNCB was applied to another site. The appearance of an erythemato-papular response 48 hr later was recorded as positive.

Statistical methods. The corrected chi-square test and Student's *t* test were used for the statistical analyses.

RESULTS

T cell studies in bacteriologically positive, non-ENL patients (Group 1)

T cell subset enumerations. T cell subsets, as analyzed by indirect immunofluorescence with OKT 3, OKT 4, and OKT 8 monoclonal antibodies are shown in Table 2. Taken as a group, these patients display increased suppressor cell and decreased helper cell percentages. Their H/S ratio is

TABLE 1. *General characteristics of the patients.*

Patient no.	Sex	Age (yr)	Site of birth or probable infection	Classification[a]	Duration of disease (yr)	Treatment during the preceding year[b]	Bacteriologic Index (Morphological Index)[c]	
Group 1. Bacteriologically positive, non-reactional patients								
1	F	22	Congo	LL	3	Rifampin	3.00	(0)
2	M	58	West Indies	LL	15	DDS	3.75	(40%)
3	F	54	West Indies	LL	12	DDS	3.25	(<1%)
4	M	30	Sénégal	LL	2	None	4.50	(40%)
5	M	24	Vietnam	BL	5	None	2.25	(2%)
6	F	18	Vietnam	BL	3	None	3.25	(20%)
Group 2. Bacteriologically negative, non-reactional patients								
7	F	23	La Réunion	LL	6	Rifampin (stopped 6 months ago)	0.25	
8	M	62	Vietnam[d]	LL	2	Rifampin	0	
9	F	43	West Indies	LL	15	Sulforthomidine	0	
10	M	40	West Indies	LL	33	DDS	0	
11	M	51	Spain	LL	15	DDS	0	
12	M	31	Morocco	BL	18	Rifampin Clofazimine Sulforthomidine	0	
13	M	78	Vietnam[d]	BL	2	Rifampin Clofazimine Sulfamethoxy-pyridazine	0.25	
14	F	24	West Indies	BL	7	DDS	0	
15	M	40	French Guyana[d]	LL	5	Rifampin Clofazimine DDS	0.75	
Group 3. ENL patients								
16	F	21	West Indies	LL	9	None	3.50	(25%)
17	M	26	West Indies	LL	3	Rifampin Thalidomide	2.50	(10%)
18	M	35	West Indies	LL	3	Sulfamethoxy-pyridazine	0	
19	M	26	West Indies	LL	3	Rifampin Clofazimine Sulfamethoxy-pyridazine Thalidomide	2.25	(0)
20	M	38	West Indies	BL	4	Rifampin Sulforthomidine	2.25	(0)
21	M	55	Vietnam	LL	22	Sulforthomidine Clofazimine Thalidomide	2.25	(0)
22	M	41	West Indies[d]	LL	29	DDS Clofazimine	2.25	(0)
23	F	36	Madagascar	LL	11	Rifampin DDS	0	
24	M	45	West Indies	LL	24	Rifampin DDS Sulforthomidine	1.50	(0)

[a] According to Ridley and Jopling's criteria ([18]).

[b] The prescribed doses were usually: a) DDS 100 mg daily, b) rifampin 600 mg daily, c) sulforthomidine (sulfadoxine, Fanasil®) 1500 mg weekly, d) clofazimine 100 mg daily, e) sulfamethoxypyridazine 750 mg on alternate days. The regularity of intake of the drugs could not be confirmed in all cases.

[c] The Bacteriologic Index was recorded as the average count of three to five smears, from different sites, expressed using the logarithmic scale of Ridley and Hilson ([19]). When solid-stained bacilli were present, their percentage (Morphological Index) is indicated in parentheses.

[d] Caucasian origin.

TABLE 2. *T cell subset distribution in lepromatous patients and healthy controls. Data presented as mean ± S.E.M.*

Subjects (no.)	Percent positive cells among circulating mononuclear cells			Percent positive cells among T cells (OKT 3+)		Ratio % OKT 4+/ % OKT 8+
	OKT 3+	OKT 4+	OKT 8+	OKT 4+	OKT 8+	
Controls (41)	66.7 ± 1.7	41.4 ± 1.4	25.7 ± 1.3	63.0 ± 2.2	38.7 ± 1.8	1.80 ± 0.13
Group 1 Bacteriologically positive, non-reactional (6)	66.1 ± 3.5	33.5 ± 4.81[b]	33.6 ± 4.0[b]	49.9 ± 5.9[b,d]	51.0 ± 5.9[b]	1.05 ± 0.18[b]
Group 2 Bacteriologically negative, non-reactional (9)	66.0 ± 4.4	41.1 ± 2.9	26.9 ± 1.83	62.6 ± 2.6	41.9 ± 3.4	1.56 ± 0.13
Group 3 ENL (9)	59.5 ± 3.9	43.0 ± 2.9	17.4 ± 2.0[a,c,e]	74.5 ± 6.8[b,f]	27.2 ± 4.0[a,d,e]	2.77 ± 0.39[a,c,e]

[a] Different from Control Group ($p < 0.01$).
[b] Different from Control Group ($p < 0.05$).
[c] Different from Group 2 ($p < 0.01$) and from Group 1 + Group 2 ($p < 0.01$).
[d] Different from Group 2 ($p < 0.05$).
[e] Different from Group 1 ($p < 0.01$).
[f] Different from Group 1 ($p < 0.05$).

significantly lower than the H/S ratio in controls.

Functional studies. Five patients had skin tests to four antigens unrelated to *M. leprae*. The mean of their responses was 6.2+ which was significantly lower than controls ($p < 0.01$). Four patients were challenged with DNCB and only one could be sensitized. Only two patients had LTT to PHA, Con-A and PWM. LTT were normal in one patient and markedly depressed in one (41%, 15%, and 23% of control values for PHA, Con-A, and PWM, respectively).

T cell studies in bacteriologically negative, non-ENL patients (Group 2)

T cell enumerations. As shown in Table 2, T cell subsets in this group of patients are normally distributed.

Functional studies. Skin tests to four antigens unrelated to *M. leprae* were performed in six patients. They had a mean response of 4.6+, significantly lower ($p < 0.01$) than the controls' responses. Four patients were tested for DNCB sensitization. None could be sensitized.

LTT to PHA, Con A, and PWM were performed in five patients. The proliferative responses were diminished. Only the response to PHA, however, was significantly decreased ($p < 0.01$). Con-A-induced suppressive activity was studied in four patients and found normal.

Correlation between the bacterial load and the distribution of T cell subsets in non-ENL patients

Since the results of T cell subset enumerations were different in bacteriologically positive (Group 1) and bacteriologically negative (Group 2) non-reactional lepromatous patients, pointing to a possible relationship between the bacterial load and the balance between circulating T helper and T suppressor cells, we investigated this point further.

Four patients from Group 1 were treated, after the initial evaluation, by an efficient antibacterial therapy and had serial measurements of their T cell subsets and bacterial load (Table 3). In this group, a negative correlation was found between the Bacteriologic Index (BI) and the H/S ratio ($r = -0.61$, $p < 0.05$). A more significant

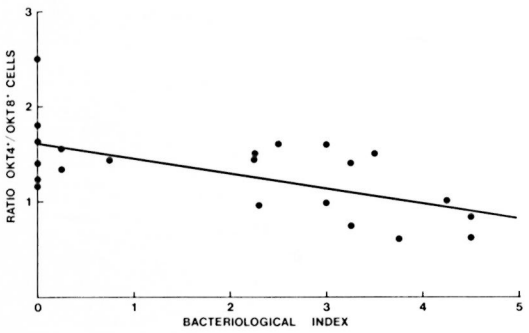

FIG. 1. Correlation between BI and H/S ratio in non-reactional patients (Groups 1 and 2). Correlation is statistically significant ($p < 0.005$).

correlation exists when data from Group 1 and Group 2 patients are pooled ($r = -0.61$; $p < 0.005$). Figure 1 shows the regression line for Group 1 and Group 2 patients.

We had the opportunity to follow a patient whose observation illustrates the correlation between the BI and the H/S ratio. He was on dapsone monotherapy for 15 years for lepromatous leprosy; his BI was 0; and his H/S ratio was 1.41. Nine months later he suffered a relapse due to DDS-resistant bacilli (proved by mouse foot pad inoculation). His BI was 3.75+ (patient 2, Table 1) and his H/S ratio was 0.60. A combined therapy using rifampin, ethionamide, and clofazimine was administered daily. One month later his BI was 3 and the H/S ratio, 0.97; three months later, his BI was 2.50 and the H/S ratio, 1.60 (Fig. 2).

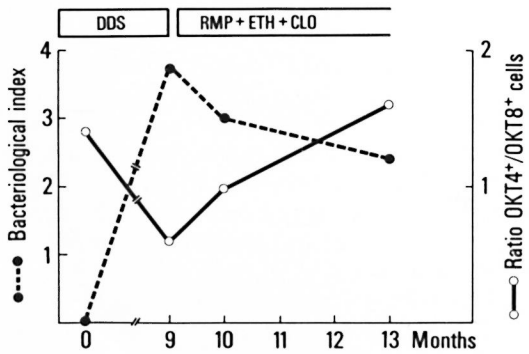

FIG. 2. Inverse relationship between bacterial load and H/S ratio for patient studied at the time of efficient DDS therapy and also during a relapse due to DDS-resistant bacilli, and then subsequent to efficient combined therapy (rifampin + ethionamide + clofazimine).

TABLE 3. *The Bacteriologic Index and OKT 4+/OKT 8+ ratio in non-reactional lepromatous patients.*[a]

Patients (no.)	Bacteriologic Index	% OKT 4+/ % OKT 8+
1	3.00	1.60
	2.30	0.96
2	3.75	0.60
	3.00	0.97
	2.50	1.60
3	3.25	0.74
	2.25	1.50
4	4.50	0.61
	4.50	0.83
	3.50	1.50
	4.25	1.00
5	3.25	1.29
6	2.25	1.44
7	0.25	1.50
8	0	1.17
9	0	1.23
10	0	1.40
11	0	2.50
12	0	1.80
13	0.25	1.33
14	0	1.64
15	0.75	1.43

[a] Data from the initial study of Group 2 patients and of the initial and serial studies of Group 1 patients were used to calculate the correlation between the bacterial load and the T cell subset distributions in non-ENL patients. The corresponding correlation is shown in Figure 1.

T cell studies in ENL patients (Group 3)

T cell subset enumeration. As shown in Table 2, results of T cell subset enumerations in ENL patients, either bacteriologically positive or not, differ from results in non-reactional patients. ENL patients have decreased percentages of OKT 8^+ cells ($p < 0.01$) with a significant increase of the H/S ratio. Furthermore, in ENL patients there is no correlation between the BI and the H/S ratio ($p = 0.52$).

Functional studies. Nine patients in Group 3 had skin tests. Their mean response (5.16+) was significantly lower than that of controls. Sensitization to DNCB was attempted in seven patients and successful in five. The number of DCNB-responders

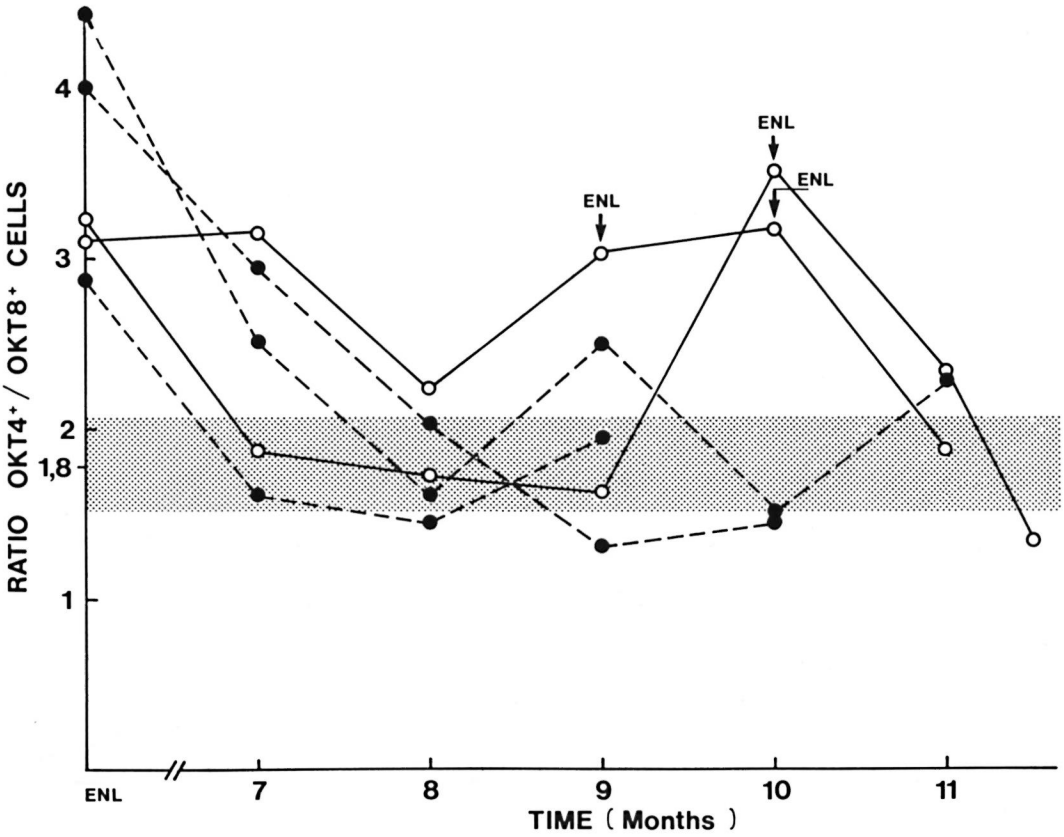

FIG. 3. H/S ratio evaluated in five patients at the time of initial ENL (time 0) and a few months later. Three patients (---●---●---) remained free of recurrences; two (—○—○—) had recurrences. Grey zone indicates normal values (1.80 ± 0.13).

among ENL patients is higher than among non-ENL patients (Groups 1 and 2), but the difference is not significant ($p = 0.06$). LTT were performed in eight patients. Mean proliferative responses were elevated. PHA-induced proliferation was 128%, Con-A-induced proliferation was 122%, and PWM-induced proliferation was 178% of simultaneously tested controls. Con-A-induced suppressive activity was measured in five patients. It was normal in two, and markedly depressed in three.

Sequential T cell subset enumerations. Since ENL patients appeared strikingly different from non-reactional patients, we tried to find out whether these patients had a permanently different immune status than non-reactional patients, or whether these perturbations in T cell subset distributions were transient. Five patients from Group 3 could be evaluated again, from the sixth to the eleventh month following their initial ENL. Results of the sequential evaluation of T cell subsets are shown on Figure 3. It can be seen that in all the patients who remain free of ENL, the H/S ratio decreases in nine months or less. Conversely, when patients undergo ENL recurrences, the H/S ratio rises again.

DISCUSSION

The evaluation of the proportions of circulating T cell subsets by the monoclonal antibody technique is a valuable method for delineating T cell imbalances in a number of immunological diseases ([3]). Since it has been previously shown that *M. leprae* induces T cell mediated suppression of immune responses ([8, 22]), we investigated T cell subsets in lepromatous leprosy. Using the monoclonal antibody technique, we observed that circulating helper and suppressor T cells vary greatly in lepromatous leprosy, according to the clinico-bacteriological

status of the patients. A heavy bacterial load is associated, in non-reactional patients, with an increase in T suppressor cell percentages. We could demonstrate a statistical correlation between the H/S ratio and the BI. In bacteriologically negative patients, the H/S ratio returns to normal values. In spite of normal T cell subset distributions, bacteriologically negative patients in our study still display some impairment of CMI. It must be remembered that mechanisms other than suppressor cells may contribute to impaired CMI, *e.g.*, suppressor macrophages ([4, 13]) and circulating inhibitory factors ([9]). It can be hypothesized that T suppressor cells are active in lepromatous leprosy, and that they are responsible for at least a part of the CMI impairment. These cells could be generated in response to the infection by *M. leprae* ([4, 10]) and a correlation between the bacterial load and the T cell dependent functions has already been shown in lepromatous patients by Nath, *et al.* ([12]). Mehra, *et al.* ([11]) demonstrated that a particular T cell subset, termed $TH2^+$, is responsible for the lepromin-induced suppression exerted *in vitro* by lymphocytes from lepromatous patients. The $TH2^+$ subset has been identified as OKT 8^+ cells ([16]).

ENL is usually considered a manifestation of Arthus' phenomenon ([24]). Our previous results have demonstrated that ENL patients display different CMI parameters than non-ENL patients ([2]). In ENL patients, decreased OKT 8^+ percentages are associated with increased mitogen responsiveness and increased cutaneous DNCB reactions. Such an augmentation of immune responses in ENL has already been mentioned ([1, 8, 14, 23]). The diminution of circulating T suppressor cells in ENL patients is not a permanent finding. In patients who remain free of ENL for a few weeks, normalization of the H/S ratio occurs.

The effects of the various drugs taken by leprosy patients, including rifampin, dapsone, thioamides, clofazimine and thalidomide, on the circulating T cell subsets is not precisely known. In our experience, we did not see any influence of a particular drug on the T cell distribution.

Our results suggest that a dysregulation T cell mediated control of immune responses might play an important role in the various events encountered in lepromatous leprosy. In many of the individuals suffering from a heavy bacterial load, an increase in suppressor cells is associated with diminished immune functions. When an efficient therapy has reduced the bacterial load, suppressor cells return to normal, though some degree of CMI impairment may persist. These patients do not develop ENL. In our study, patients with ENL do not increase their T suppressor cells, even when they are heavily infected. Their cell-mediated immune functions are not impaired, and may even be higher than normal.

ENL could thus be considered as a disease of insufficient T cell mediated suppression. The lack of suppression results in the well known exaggeration of B cell responses (high antibody titers, immune complex deposition and complement activation) and in the increase we observed in T cell responses. However, the CMI deficiency towards *M. leprae* antigens remains unchanged.

The hypothesis that the immune dysregulation in ENL is due to the inability to develop suppressor cells after infection with *M. leprae* may permit another approach to the understanding of the pathogenesis of ENL.

SUMMARY

Circulating T cells, T helper, and T suppressor cells were investigated in 24 lepromatous patients, using murine hybridoma-derived monoclonal antibodies OKT 3, OKT 4, and OKT 8. Six bacillary lepromatous patients without recent ENL were studied; in this group, suppressor cells were increased and helper cells diminshed, resulting in a decrease in the helper/suppressor (H/S) ratio. Nine bacteriologically negative lepromatous patients without recent ENL were studied. T cell subsets distribution was normal, although some T cell functions were affected. It was further shown that in non-ENL patients, the diminution of the H/S ratio is correlated with the Bacteriologic Index (BI). Although bacillary, ENL patients exhibit a completely different T cell pattern than non-reactional patients. In these patients, there was a significant diminution of circulating suppressor cells, and an increase in T cell functions. These abnormalities were transient.

Our results confirm the importance of suppressor cells in lepromatous leprosy, and suggest that imbalance between helper and suppressor cells may play a role in the pathogenesis of ENL reactions.

RESUMEN

Se midieron los niveles de los linfocitos T circulantes, T cooperadores y T supresores, en 24 pacientes lepromatosos, usando anticuerpos monoclonales (OKT 3, OKT 4 y OKT 8) derivados de hibridomas murinos. Se estudiaron 6 pacientes lepromatosos bacilares sin ENL reciente y se encontró que las células supresoras (S) estuvieron incrementadas en tanto que las células cooperadoras (H) estuvieron disminuídas, dando como resultado un valor bajo en la relación cooperación/supresión (H/S). También se estudiaron 9 pacientes bacteriológicamente negativos, lepromatosos, sin ENL reciente. Se encontró una distribución normal de las subpoblaciones de las células T, aunque algunas funciones de estas células se vieron afectadas. Además, se demostró que en los pacientes sin ENL la disminución en la relación H/S estuvo relacionada con el Indice Bacteriológico. Aunque bacilares, los pacientes con ENL exhibieron un patrón de células T completamente diferente al de los pacientes no reaccionales. En estos pacientes hubo una significante disminución de las células supresoras circulantes y un aumento en las funciones de las células T, aunque estas anormalidades fueron transitorias. Nuestros resultados confirman la importancia de las células T supresoras en la lepra lepromatosa y sugieren que el desbalance entre cooperación y supresión puede jugar algún papel en la patogénesis de las reacciones tipo ENL.

RÉSUMÉ

Chez 24 malades lépromateux, on a étudié les cellules T circulantes, les cellules T "helper," et les cellules T "suppressor," en utilisant des anticorps monoclonaux murins OKT 3, OKT 4 et OKT 8, dérivés à partir d'hybridomes. On a étudié 6 malades lépromateux bacillaires, n'ayant pas présenté récemment d'érythème noueux lépreux. Dans ce groupe, les cellules-"suppressor" étaient augmentées, et les cellules-"helper" étaient diminuées, ce qui entraînait une diminution du rapport "helper"/"suppressor" (H/S). Par ailleurs, neuf malades lépromateux bactériologiquement négatifs, également sans ENL récents, ont été étudié. La distribution des sous-populations de cellules T était normale, quoique certaines fonctions des cellules T étaient affectées. On a en outre montré que, chez les malades sans ENL, la diminution du rapport H/S présentait une corrélation avec l'Index Bactériologique. Quoique présentant des bacilles, les malades atteints d'ENL témoignaient d'un profil totalement différent des cellules T, lorsqu'on les comparait aux malades sans réaction. Chez ces malades, on a observé une diminution significative des cellules "suppressor" en circulation, et une augmentation des fonctions des cellules T. Ces anomalies étaient transitoires. Les résultats publiés ici confirment l'importance des cellules "suppressors" dans la lèpre lépromateuse; ils suggèrent également qu'un déséquilibre entre les cellules "helper" et "suppressors" peut jouer un rôle dans la pathogénèse des réactions d'érythème noueux lépreux.

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