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Histologic Responses in Sixty Multibacillary Leprosy Patients Inoculated with Autoclaved *Mycobacterium leprae* and Live BCG[1]

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Previous publications ([2, 4–6]) have drawn attention to the immunotherapeutic effects of a mixture of *Mycobacterium leprae* and BCG on lepromatous (LL) and borderline lepromatous (BL) patients. Results demonstrate that the defect in cell-mediated immunity (CMI) in these forms of leprosy is not irreversible and can be overcome by immunotherapy. Futhermore, Mitsuda conversion can be achieved in Mitsuda-negative contacts and in some patients with indeterminate leprosy. The relevance of these studies to current research on leprosy vaccines has been summarized ([3]).

For more than a decade, numerous biopsy specimens from leprosy patients undergoing immunotherapy in Caracas, Venezuela, have been evaluated, both before and after entry into trials. Routine histopathologic diagnoses on these specimens have corresponded to the clinical and immunologic changes in most patients, and a preliminary analysis ([3]) indicated that after immunotherapy a high percentage of LL and BL patients changed in the histopathologic classification toward tuberculoid disease. Because of the relevance of the histopathologic findings to the overall interpretation of immunotherapeutic studies, serial biopsy specimens from a representative group of patients were submitted for study to an international group of histopathologists experienced in leprosy. This group met in Caracas in December 1982. This paper describes the results of this workshop and discusses the implications of the findings for the immunotherapy of leprosy with a mixture of *M. leprae* and BCG.

MATERIALS AND METHODS

Although 351 active LL and BL patients had been vaccinated, many three or more times, it was impossible for all participants on the occasion of the workshop to examine each of the nearly 1000 biopsy specimens accrued from these patients. Of the 351 patients, only 115 had been observed long enough to have sufficient serial biopsy specimens and clinical evaluations to warrant consideration by the workshop. Because of time constraints, the workshop participants decided to study a random selection of 60 patients. Biopsy specimens from these 60 patients had been taken prior to and following immunotherapy. Specimens of Mitsuda reactions from some patients were evaluated histopathologically. The patients were all Venezuelan adults, 47 males and 13 females. All patients had been classified on entry to the trial as either LL or BL according to the Ridley-Jopling system ([9]).

The vaccine was composed of autoclaved *M. leprae* from experimentally infected armadillos and viable BCG (Institut Pasteur, Paris) ([3]). The *M. leprae* were purified by the Draper 1/79 method ([7]). Each dose of vaccine contained 6×10^8 leprosy bacilli in a volume of 0.4 ml plus 0.1 ml of BCG in varying concentrations, depending on the patient's cutaneous response to purified protein derivative (PPD). The vaccine was given by intradermal injection: 0.5 ml was distributed in three sites in the deltoid and upper back regions. Vaccination schedules and follow-up procedures on the patients

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TABLE 1. *Antileprosy drug treatment history of 60 patients with lepromatous (LL) or borderline lepromatous (BL) leprosy.*

Patient no.	Early treatment	Recent treatment	Treatment at beginning of immunotherapy
1.	1978: DDS[a]-O[b] + R[c]	1979: DDS-O + R	1980: Same
2.	1977: DDS-I[d] + R	1979: DDS-O + C[e]	1980: Same
3.		1981: DDS-O + C	1981: DDS + R
4.	1978: DDS-I + C	Same	1981: NT[f]
5.	1979: DDS-I	1980: DDS-O + R	1981: C
6.		1979: DDS-I	1981: NT
7.	1978: DDS-I	1979: DDS-O + R + C	1981: NT
8.			1981: DDS-O + R
9.	1951: DDS-O	1960–1980: NT	1980: DDS-O + R
10.			1981: DDS-O + R
11.		1979: DDS-I + R	1982: Same
12.	1979: DDS-I	Same	1982: Same
13.	1969: DDS-O	Same	1981: Same
14.	1978: DDS-O + R	Same	1979: NT
15.	1979: DDS-I + R	DDS-I	1981: NT
16.	1970: DDS-O	DDS-O	1981: Same
17.			1980: NT
18.		1980: DDS-O + C + R	1981: DDS-O + C
19.			1981: NT
20.			1981: NT
21.	1954: DDS-O	Same	1981: DDS + R
22.	1963: DDS-O	1979: DDS-I	1980: DDS + C
23.	1978: DDS-I	1979: DDS-I + R	1980: Same
24.	1961: DDS-O	1972: DDS-I + R	1980: Same
25.	1978: DDS-I	1979: DDS-O + C	1980: Same
26.	1951–1953: DDS-O 1953–1966: NT 1966: DDS-O	1979: DDS-O	1980: Same
27.	1972: DDS-O	1979: DDS-O + C	1981: NT
28.	1955: DDS-O	1979: DDS-I	1981: DDS-I
29.	1963: DDS-O	1979: Same	1981: NT
30.		1980: DDS-I + R	1981: Same
31.	1969: DDS-O	1979: DDS-I	1980: DDS-O + R
32.		1981: DDS-O + R	1981: Same
33.		1980: DDS-O + R	1981: NT
34.	1953–1955: DDS-O 1955–1978: NT 1978: DDS + R	DDS + C	1980: Same
35.		1979: DDS + R	1980: NT
36.	1978: DDS-O + R	1979: C	1980: DDS-O + R
37.	1961: DDS-O 1973: DDS-O + C 1974: DDS-I + C	1979: DDS-I + R	1981: Same
38.		1979: R	1981: DDS-I + R
39.		1979: DDS-O + R	1980: Same
40.	1973: DDS-O + R 1975: DDS-O	1979: DDS-O + R	1980: Same
41.		1981: DDS-O + R	1981: Same
42.		1979: DDS-I + R	1981: DDS-O + R
43.			1980: DDS-O + R
44.		1980: DDS-I + R	1981: Same
45.	1976: DDS-O 1977: DDS-O + R	Same	1981: NT
46.	1970–1974: DDS-O	1980: DDS-I	1980: Same
47.		1980: DDS-O + R	1981: DDS-O
48.	1969–1975: DDS-I	1980: DDS-O + R	1980: DDS-O
49.		1979: R	1981: NT
50.	1976: DDS-I 1978: DDS	Same	1982: Same
51.	1977: C + R		1980: NT
52.		1979: DDS-O + R	1980: Same
53.	1975–1978: DDS-I	1979: DDS-O + R	1980: Same
54.			1980: DDS-O + R
55.		1979: DDS-I	1980: NT
56.		1980: DDS-O + R	1980: NT
57.			1981: DDS-O + R
58.	1975: DDS-I	DDS-O	1981: Same
59.		1979: DDS-O	1980: C
60.	1978: DDS-I	1980: DDS-O	1981: Same

[a] DDS = dapsone.
[b] DDS-O = oral dapsone
[c] R = rifampin.
[d] DDS-I = inject. dapsone. The injectable dapsone (DDS) preparation used in Venezuela since the early 1960s has been supplied by Bristol Laboratories Corporation, Syracuse, New York, U.S.A. and contains 250 mg DDS per mil. Originally it contained aluminum monostearate, but lately only suitable wetting agents. The maximum adult dose was 4 ml (1 g DDS) at monthly intervals, but dosage was started at 0.25 ml and increased by 0.25 ml to full dosage.
[e] C = clofazime.
[f] NT = no treatment.

TABLE 2. *Initial classification and post-treatment changes in 60 leprosy patients treated with immunotherapy.*

Grading system	Initial biopsy (1)	Later biopsies (2)	(3)	(4)	Biopsy with greatest changes
No. cases studied	60	60	56	32	60
Total score assigned[a]	30,773	22,534	17,690	10,204	17,894
Total opinions recorded	336	331	283	155	301
Average points per patient per observer	91.6	68.1	62.5	65.8	59.4
Classification according to points scale[a]	LL	BB	BB	BB	BB

[a] See text for point values assigned to Ridley-Jopling classes.

have been published ([3]). All but 6 of the 60 patients evaluated had received previous treatment with antileprosy drugs and, as can be seen from Table 1, this usually consisted of dapsone monotherapy given monthly by intramuscular injection. This therapy was commonly employed in Venezuela in the 1960–1980 era. In spite of treatment with antileprosy drugs, all patients were clinically and bacteriologically active in varying degrees. Seventeen patients were not on treatment at the beginning of immunotherapy because of intolerance to dapsone or because of serious erythema nodosum leprosum (ENL) reaction. With the exceptions of patients 17, 19, 20, and 25 (Table 1), drug treatment during immunotherapy and subsequently consisted of multiple drug therapy (MDT) with dapsone, clofazimine, and rifampin. Patient 25 left Venezuela and there is no follow-up for this case.

During the more than 30 years' experience of the leprosy service of the Instituto Nacional de Dermatologia in Caracas, very few reversal reactions have been recorded in patients treated with sulfones. Likewise, in 238 LL and BL patients treated by MDT, during the period 1979–1985 there have been no reversal reactions.

Hematoxylin-eosin (H&E) and Fite-Faraco-stained sections of pre-treatment and post-treatment biopsy specimens, appropriately identified as to patient's name and number and sequence, were presented to each participant. No other information was available to the histopathologists at the time the specimens were being evaluated. Each participant recorded his findings independently on a standard form, giving a description of the histopathologic changes and classification of the initial and later biopsy specimens, using the five symbols of the Ridley-Jopling system (LL, BL, BB, BT or TT). The trays of slides were circulated among the participants over 5 working days, and the reports collected and tabulated by a clerk on a form that included data on the Mitsuda reaction biopsy specimens (where appropriate), the size of the Mitsuda reaction (in mm), and the result of skin tests with soluble protein antigen of *M. leprae* (positive or negative). To permit a statistical analysis, the classes of the Ridley-Jopling system were given numerical values as follows: LL and LL_s = 100; BL = 80; BB = 60; BT = 40; TT = 20. The very few specimens reported as "indeterminate" were assigned a value of 20. In the one biopsy specimen noted as "not leprosy" or "no evidence of leprosy" a value of 0 was assigned. This patient showed no clinical evidence of leprosy.

The six participants recorded 1105 observations out of a possible 1248, and the group findings were then brought together on a single master form for further analysis. To establish a statistical value representing the consensus of the six observers, points were allocated as follows: 90–100 for LL; 70–89 for BL; 50–69 for BB; 30–49 for BT; 10–29 for TT or indeterminate; 0–9 for "not leprosy." Where combined classifications were indicated, the sum of half of the value of each class was employed, e.g., LL/BL = 90.

RESULTS

In Table 2, we analyze the overall data on the 60 patients studied, giving a global sum score for all histopathologists, total opinions recorded for each patient, and the average of points per case for each observer.

TABLE 3. *Changes in classification of patients treated with immunotherapy according to their initial histopathological classification of LL or BL.*

Grading system	Initial biopsy (1)	Later biopsies (2)	(3)	(4)	Biopsy with greatest changes
	LL patients				
No. cases studied	42	42	38	22	42
Total score assigned[a]	22,470	16,200	12,020	8,060	13,130
Total opinions recorded	235	232	189	113	217
Average points per patient per observer	95.6	69.8	63.6	71.3	61.4
Classification according to points scale[a]	LL	BB	BB	BL	BB
	BL patients				
No. cases studied	18	18	18	10	18
Total score assigned[a]	8,303	6,334	5,670	2,144	4,764
Total opinions recorded	101	99	94	42	87
Average points per patient per observer	82.2	64.0	60.3	51.0	54.8
Classification according to points scale[a]	BL	BB	BB	BB	BB

[a] See text for point values assigned according to Ridley-Jopling classes.

The last value was used to assign the position of the patient in the Ridley-Jopling classification of the spectrum of leprosy. The initial grading of the group gave an average point value of 91.6, or LL, and decreased to a minimum of 59.4 points, or BB, placing the histopathologic class in the mid-borderline area.

In Table 3, using the same method, we record the evolution of the 42 patients initially classified as LL and the 18 patients as BL. The initial grading of the LL patients was 95.6. If the sequential biopsy specimens with the greatest changes are considered, the grade is 61.4, or BB, representing a reduction of 35.8%. By a similar assessment, the 18 patients classified as BL changed from 82.2 to 54.8 points, for a change of 33.9%.

The classification of all initial specimens and the changes observed in later specimens are shown in Table 4. Here we see the overall evolution in all 60 patients, from an initial distribution of 70% LL and 30% BL to a concentration centered mainly in BB forms (55% of all cases). An additional 20% of the patients evolved toward BT, while 4 of 42 (6.7%) remained LL and 3 of 18 (16.7%) remained BL. Note that in LL patients the third sequential specimens show a slight shift back toward LL; however, the significance of this compared to the first follow-up specimen is doubtful, and specimens from only 22 patients were available. For BB patients there is consistent improvement over the study period. There were no clinical, histologic, or bacteriologic relapses during the period. Immunotherapy was continued in this series of patients until the last biopsy specimen was taken.

Because of an anticipated potential for damage to peripheral nerves in patients undergoing reversal reactions, cutaneous nerves were routinely examined in all biopsy specimens. In patients undergoing reversal reactions, or those who had upgraded even to BT, the nerves were remarkably well preserved.

Biopsy specimens from only four post-immunotherapy Mitsuda reactions were studied, a number too small to draw any conclusions. However, all histopathologic

TABLE 4. *Changes in initial classification of LL and BL patients treated with immunotherapy.*

Later specimen	Initial specimen: LL No.	LL %	BL No.	BL %	Total No.	Total %
LL	4	9.5	—	—	4	6.7
BL	7	16.7	3	16.7	10	16.7
BB	24	57.1	9	50.0	33	55.0
BT	7	16.7	5	27.8	12	20.0
TT	—	—	—	—	—	—
NL[a]	—	—	1	5.5	1	1.7
Total	42	100.0	18	100.0	60	100.0

[a] No evidence of leprosy in biopsy specimen.

TABLE 5. *Uniformity of histopathologic classification of initial specimens among all observers.*

Observer[a]	Patients classified	Classification of examined specimens (%)					Total
		LL[b]	BL	BB	BT	TT	
1	60	80.0	20.0	0	0	0	100
2	36	50.0	33.3	13.9	2.8	0	100
3	60	61.7	38.3	0	0	0	100
4	60	55.0	43.3	1.7	0	0	100
5	60	80.0	16.6	1.7	1.7	0	100
6	60	71.7	28.3	0	0	0	100

[a] Order of listing of observers is neither according to order of authors nor alphabetic.
[b] Includes specimens classified as subpolar lepromatous (LL_s).

changes in these specimens correlated well with the concurrent findings in the lesions in the same patient.

The comparability among the six participants of the histopathologic classification of the initial specimens from all patients is shown in Table 5.

DISCUSSION

It was recognized at the outset of the workshop that the studies that began in 1970 on the immunotherapy of leprosy at the Instituto Nacional de Dermatologia developed without the benefit of a prospective trial. Thus, clinical and laboratory data were not available on all patients treated with immunotherapy. It is of particular interest that all 60 patients in this series and others in the total group of 351 had received chemotherapy before starting immunotherapy and that, in most instances, the chemotherapy continued during immunotherapy. While from a purely scientific viewpoint it would have been preferable to observe changes in a group of patients without chemotherapy, this was considered unethical and was never attempted. Despite these reservations, on the basis of several decades of experience in clinical leprosy by the Instituto Nacional de Dermatologia, reversal (upgrading) reactions have not been observed in properly classified LL patients under chemotherapy alone, and such reactions are rare in BL patients. This is certainly the case with dapsone monotherapy. Many of the patients in this study entered when they had already been treated for some time (Table 1) and essentially all of their baseline Mitsuda and *M. leprae* soluble protein antigen skin tests were negative. More recent observations of a similar nature on patients undergoing MDT are comparable to those who received dapsone monotherapy.

The essential finding of this workshop is that, following immunotherapy, a considerable percentage of all biopsy specimens from LL and BL patients showed upgrading toward tuberculoid disease. Applying the criteria of Ridley ([8]), in some patients this upgrading was accompanied by or passed through reactional episodes. Even in those patients in whom no such reactional features were obvious, the change in classification from LL or BL toward tuberculoid leprosy was marked. Although 53% of the 60 patients (88.3%) upgraded following immunotherapy, there was an apparent clustering in the mid-borderline area (Table 4), with 55% of all cases being re-classified as BB after immunotherapy.

This project was arranged and directed primarily toward the classification and assessment of skin-biopsy specimens from patients undergoing immunotherapy. However, after evaluating the tissue specimens, all participants had the opportunity to examine many of the study patients, together with the case records and sequential clinical color transparencies. This revealed the extent and intensity of reversal (upgrading) phenomena in the skin (Figs. 1–4), and confirmed previous observations from this Center that there is a remarkable lack of serious neural involvement in these patients, even during periods of reaction requiring steroid treatment. We have no explanation for this observation, though it may be related to the way antigens of *M. leprae* are presented to the patient in the immunotherapy procedure. It has already been shown ([1]) that there is antigen heterogeneity in patients with reactions in borderline lep-

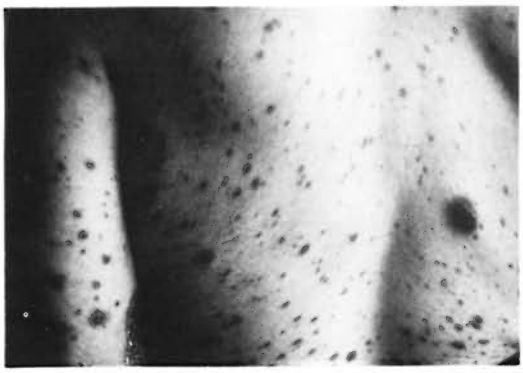

FIG. 1. Reaction to immunotherapy in Patient #58 on 12 December 1982, showing multiple erythematous papules and plaques. Immunotherapy was started in February 1982. AFIP Neg. #87-7098.

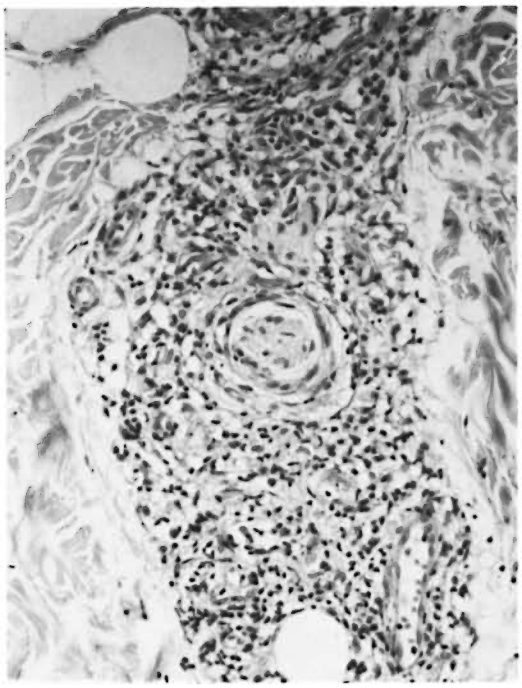

FIG. 2. Initial biopsy specimen of skin from patient in Figure 1, showing foamy histiocytes mixed with moderate numbers of lymphocytes. A few histiocytes showed early epithelioid cell changes. The perineurium is thickened. Composite point score on this specimen taken on 26 February 1982 was 88, placing specimen in the BL area, near to LL (H&E ×250). AFIP Neg. #84-9012.

rosy, with the balance of skin and nerve lesions being related to the use of either whole or sonicated preparations of the bacillus. Differences in antigen-presenting cells could also be crucial (Bjune, personal communication to ACMc, 1982). Skin macrophages are able to present antigen in combination with HLA-D antigens, a prerequisite for a delayed-type hypersensitivity response. However, the ability of Schwann cells to present antigen has not been established. In prospective trials of patients undergoing immunotherapy, both nerves and skin should be evaluated clinically and histopathologically.

SUMMARY

Sixty lepromatous or borderline lepromatous patients were submitted to immunotherapy with a mixture of autoclaved *Mycobacterium leprae* and BCG. The histopathologic findings in skin biopsy specimens taken before and after immunotherapy were evaluated independently by six histopathologists in a workshop setting. Their pooled observations on diagnosis and classification were analyzed to assess the histopathologic changes following various periods of immunotherapy. Expressing the results as the average value of five to six independent observations, there were changes in classification of reversal or upgrading toward the tuberculoid end of the leprosy spectrum in 90.5% of the patients initially classified as lepromatous (LL), and in 83.3% of those initially classified as borderline lepromatous (BL). The histopathologic findings amply support the clinical, bacteriologic and immunological changes following immunotherapy from LL or BL, to BL, mid-borderline (BB) or even borderline tuberculoid (BT) leprosy.

RESUMEN

Sesenta pacientes lepromatosos o sublepromatosos (BL) fueron sometidos a inmunoterapia con una mezcla de *Mycobacterium leprae* autoclaveado y BCG. Los hallazgos histopatológicos en biopsias de piel tomadas antes y después de la inmunoterapia fueron evaluadas independientemente por 6 histopatólogos. Las observaciones de todos ellos sobre el diagnóstico y la clasificación se analizaron para establecer los cambios histopatológicos a diferentes períodos de inmunoterapia. Expresando los resultados como el valor promedio de 5 a 6 observaciones independientes, hubieron cambios en la clasificación hacia el extremo tuberculoide del espectro de la lepra en el 90.5% de los pacientes inicialmente clasificados como lepromatosos (LL) y en el 83.3% de aquellos inicialmente clasificados como sub-

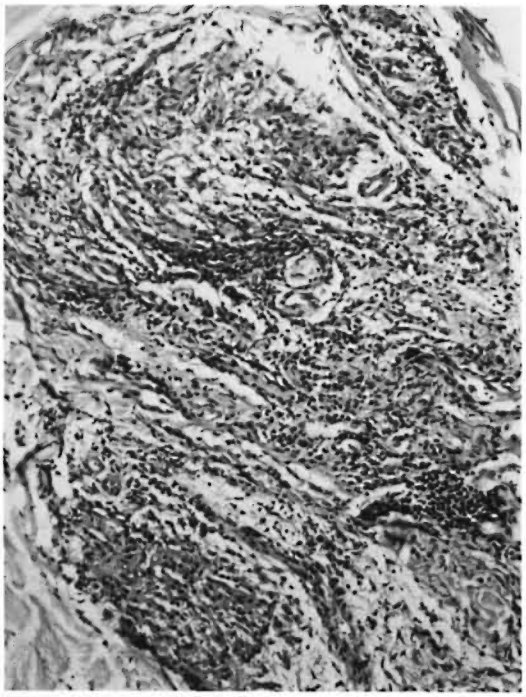

FIG. 3. Biopsy specimen of skin from patient in Figure 1 taken on 24 May 1982, following immunotherapy. Cellular infiltration is composed of scattered foci of epithelioid cells with large numbers of lymphocytes. There are occasional vacuolated histiocytes. Although the perineurium of nerves was obliterated, the nerves are otherwise normal. Composite point score on this specimen was 48, placing lesion in the BT area (H&E ×160). AFIP Neg. #84-9014.

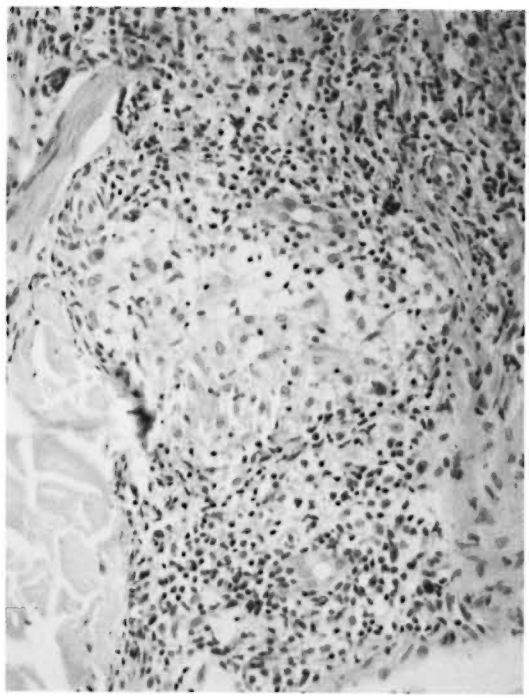

FIG. 4. Same section of skin as Figure 3, showing a rather well-formed epithelioid cell granuloma surrounded by a mantle of lymphocytes. A few vacuolated histiocytes remain within the granuloma (H&E ×250). AFIP Neg. #88-6091.

lepromatosos (BL). Los hallazgos histopatológicos apoyan ampliamente los cambios clínicos, bacteriológicos e inmunológicos que siguen a la inmunoterapia de los casos LL o BL, quienes viran a los tipos BL, BB y aún al BT de la lepra.

RÉSUMÉ

Soixante malades atteints de lèpre lépromateuse ou de lèpre lépromateuse dimorphe, ont été soumis à une immunothérapie par un mélange de *Mycobacterium leprae* autoclavé et de BCG. Les observations histopathologiques relevées dans le échantillons de biopsies cutanées prélevés avant et après l'immunothérapie, ont été évalués de manière indépendante par six histopathologistes. Leurs observations, une fois groupées pour le diagnostic et la classification, ont été analysées au cours d'un atelier pour évaluer les modifications histopathologiques à différents intervalles de temps après l'immunothérapie.

Lorsque les résultats sont exprimés comme la valeur moyenne de cinq à six observations indépendantes, peu de modifications ont été notées dans la classification des réactions réverses ou dans le glissement vers le pôle tuberculoïde du spectre de la lèpre, chez 90,5% des malades initialement classés comme lépromateux (LL), et chez 83,3% de ceux qui avaient été classés au début comme atteints de lèpre lépromateuse dimorphe (BL). Ces observations histopathologiques confirment de manière nette les modifications cliniques, bactériologiques et immunologiques qu'entraîne l'immunothérapie, qui indique un glissement des formes LL ou BL aux formes BL, dimorphe pure (BB), ou même tuberculoïde dimorphe (BT).

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