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Lymphoblastic Lymphoma in Adolescents and Adults. Clinical, Pathological and Prognostic Evaluation

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Abstract—*Sixty-four adult patients with lymphoblastic lymphoma (LB) identified according to Kiel Classification were analyzed retrospectively. Three distinct clinical presentations were identified: prevalent abdominal disease* (29 pts = 45.3%), *prevalent mediastinal disease* (14 pts = 21.9%) *and prevalent superficial node involvement* (21 pts = 32.8%). *On histological grounds, the patients with abdominal disease were mainly associated to "Burkitt like" cell lymphoma* (55%); *patients with mediastinal disease to convoluted cell type* (58%); *and those with superficial node disease to unclassified cell type* (48%). *Immunological studies showed a significant correlation between mediastinal disease and T phenotype* ($P = 0.0011$), *abdominal disease and B phenotype* ($P = 0.00042$), *and between superficial node disease and non-B non-T phenotype* ($P = 0.00024$). *Survival was independent of the type of clinical presentation and protocol employed but was correlated with the stage* ($P < 0.0005$), *symptoms* ($P < 0.025$), *bulky disease* ($P < 0.025$) *and bone marrow involvement* ($P < 0.025$). *Furthermore the response to therapy was strongly correlated with prognosis* ($P < 0.0001$) *with* 34.5 months *median survival for complete responders,* 9 months *for partial responders, and* 3 months *for non-responders. Four patients underwent bone marrow transplantation (three autologous and one allogeneic BMT in a patient in leukemic phase); three of them are still in CR* (18, 22 *and* 27 months *from the transplant) while one patient had an early relapse and died* 3 months *later.*

INTRODUCTION

LYMPHOBLASTIC lymphoma (LB) is a tumor with a rapid growth pattern which is one of the non-Hodgkin's lymphomas (NHL) with high grade malignancy that may be considered to have distinct clinical characteristics. Bone marrow and mediastinal involvement are the most common recognized findings [1–6]; central nervous system and blood involvement are more frequent than in other NHL [4–7]. In pediatric patients it has been established in several reports [8–10] that a stage system separates cases with mediastinal disease from those with predominant abdominal involvement. In addition, successful therapy in children [11–14] has produced an homogeneous and widely acceptable basis for management in these patients. Conversely, few reports [15–17] are available concerning the management of LB in adult patients because of the rare incidence of this lymphoma and the consequent lack of data necessary to answer questions regarding prognosis and treatment of this disease. To date, only few and selected patients have been reported [10, 18–21].

We present a retrospective analysis of a series of patients with LB lymphoma in an attempt to elucidate the clinical presentation, the risk factors affecting the prognosis and the therapeutic implications.

PATIENTS AND METHODS

Sixty-four adult and adolescent patients, observed from January 1978 to December 1983 at the Institute of Hematology "Lorenzo e Ariosto Seràgnoli" of Bologna University and the Department of Hematology of "Molinette" Hospital of Torino, entered this study. Forty-six were males

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and 18 were females (ratio 2.5 : 1) with a mean age of 38 yr (range 14–68 yr). The median follow-up was 40 months (range 14–84 months). All cases were diagnosed by histopathological examination; the majority by lymphnodes biopsies and some by bone marrow, gastrointestinal or soft tissue biopsies. Blocks of tissue, which had been obtained from lymph node, bone marrow, gastrointestinal or soft tissues biopsies, fixed in formalin or B5 and embedded in Paraplast [22], were always available. New sections were cut from them and stained according to the following methods H & E, Giemsa, P.A.S. and Gomori silver impregnation [22, 23]. The sections were independently reviewed by two observers (P.S. and R.M.T.) according to the criteria of the Kiel Classification [23, 24]. The same diagnosis was blindly made in 60/64 cases, complete consensus was achieved after reexamination of the divergent cases.

Furthermore, in 48/64 patients, immunological data were also available. In particular, immunophenotyping had been carried out at the time of diagnosis, either in cell suspensions or in frozen sections of lymphomatous nodes, by applying the panel of specific antisera and monoclonal antibodies listed in Table 1. To evidence antibodies, the immunofluorence and the ABC technique were alternately employed, according to the criteria of our Group [22, 25, 26].

The extent of the disease was defined according to the Ann Arbor System [30]. In particular all patients underwent one or in some cases two bone biopsies, 27 patients had lymphography, the other ones were excluded from this procedure because most of them had already detected marrow involvement or a large abdominal mass discovered by simple clinical examination or by CT scans. The last procedure was performed in few patients who had an abdominal isolated mass. One patient with isolated large spleen involvement underwent laparotomy with splenectomy for diagnostic and staging purpose. Lumbar puncture for the evaluation of cerebrospinal fluid was also part of the initial evaluation in all cases. In addition to the stage, the patients were identified according to the presence of symptoms and bulky disease. Symptoms ("B" patients) included the presence of fever, night sweats and/or weight loss. The disease was considered bulky when a tumour mass larger than 6 cm was recorded, whatever the site.

The patients were grouped according to three major clinical presentations: (1) prevalent mediastinal disease (bulky mediastinal disease); (2) prevalent abdominal disease including isolated intestinal mass or liver, spleen, mesenteric and retroperitoneal node involvement; (3) prevalent superficial node disease. Patients presenting CNS, blood or pleural involvement were assigned to one of the above groups according to the site where the disease was bulky.

Table 1. Specific antisera and monoclonal antibodies used in this study. For specificities of these reagents in normal lymphoid tissue and lymphoid tumours see [22, 27–29]

Reagent	Source
Anti-TdT	Bethesda Research Laboratory
OKT1	Ortho
OKT3	Ortho
OKT4	Ortho
OKT6	Ortho
OKT8	Ortho
OKT9	Ortho
OKT11	Ortho
Anti-Leu 7	Becton Dickinson
Anti-Leu 11	Becton Dickinson
B1	Coulter
J5	Coulter
Pan-B	Dako
Anti-IgM	Kallestad
Anti-η	Becton Dickinson
Anti-λ	Becton Dickinson
OKDR	Ortho
FMC7	Sera Lab
BA1	Hybritech
BA2	Hybritech

Variations in the therapy depended principally upon the time of the diagnosis and the institution where the patients were followed. In summary, patients observed before 1980 underwent CHOP [31] or BACOP [32] plus radiotherapy on bulky disease; subsequently therapy was programmed which was similar to the LSA_2-L_2 regimen employed in children by Wollner *et al.* [13], including an induction phase, CNS prophylaxis, consolidation therapy and 2.5 yr maintenance chemotherapy plus radiotherapy on "bulky" disease; more recently one patient in leukemic phase underwent bone marrow transplantation (BMT) from an HLA identical brother after the induction phase and conditioning therapy [33]; three other patients, without evidence of bone marrow involvement at diagnosis underwent intensive therapy followed by the reinfusion of the autologous bone marrow, previously cryopreserved [34].

The prognostic analysis was carried out considering clinical, histologic, immunologic and therapeutic parameters. Clinical parameters included age, sex, symptoms, stage bulky disease and the prevalent site of involvement. The latter also included the prognostic relevance of bone marrow, blood and CNS involvement at diagnosis. The prognostic relevance of therapy was studied by grouping the patients according to cyclic (CHOP or BACOP) and continuous (LSA_2L_2) treatment; the response to therapy was also considered as a

factor influencing prognosis. Survival curves were obtained by the Kaplan and Meier method [35]. Differences were evaluated by using the chi-square or log-rank tests as described by Peto *et al.* [36]. Further analysis, taking into account as covariates those parameters which resulted of some significance at univariate analysis, was performed employing the regression model as described by Cox [37].

RESULTS

Histological and immunological features (Table 2)

According to histological findings, the diagnosis of B-lymphoblastic lymphoma, Burkitt type was made in 28/64 cases, while 18/64 were proposed as T-lymphoblastic lymphoma, convoluted cell type, and a further 18/64 were described as lymphoblastic lymphoma unclassified.

At immunological analysis, 25 out of 48 examined cases displayed Burkitt-like or pre-B phenotype, 12 revealed prethymic or thymic origin, while 11 appeared to be non-B/non-T tumours [29].

Among the cases with both morphological and immunological information available, all B-lymphoblastic lymphomas, Burkitt-type [20] showed a clear-cut B-cell origin. Conversely, only 12/15 cases diagnosed at light microscopy as T-lymphoblastic lymphomas, convoluted-cell type revealed at immunophenotyping a definite T-cell nature, the remaining three consisting of non-B/non-T elements. Finally the neoplasms [13], which at microscopic analysis had been included in the group of lymphoblastic lymphomas unclassified, showed non-B/non-T, pre-B and prethymic characteristics in eight, four and one instances, respectively.

As shown in Table 2 when morphological and immunological findings were related to clinical presentation, the B-lymphoblastic lymphomas were more often associated with abdominal disease, the T-cell ones with a mediastinal mass, while most non-B/non-T (unclassified) cases presented with superficial lymph node swelling.

Clinical presentations (Table 3)

Twenty-one patients (32.8%) had prevalent superficial node involvement; the median age was 40 yr. In all cases the diagnosis was made by lymph node biopsy. Twenty-nine patients (45.3%) presented with prevalent abdominal disease: the median age was 41.4 yr. In four patients the diagnosis was made on intestinal tissue, in two patients on a biopsy of a large mass involving mesenteric nodes, in one patient on the spleen, in another on an ovaric mass, in 14 on superficial nodes which were associated to bulky abdominal disease and in seven on bone marrow biopsy performed for staging purposes in the presence of a large abdominal mass. Fourteen patients (21.9%) showed a mediastinal involvement as the prevalent manifestation; the median age was 30.7 yr. Most of them had concurrent superficial node involvement. Only one patient underwent thoracotomy for diagnostic purposes. Another patient had diagnosis on a bone biopsy.

Bone marrow, blood and CNS involvement were frequently recognized in all three different clinical presentations. In fact about 50% of the patients presented bone marrow involvement, 22% of the patients presented blood involvement at diagnosis and 14% during the course; 8% had CNS involvement at diagnosis and 20% presented it during the course.

Independently of the clinical presentation, the majority of the patients had disseminated disease; 80% of the patients had stage III–IV and 20% had stage I–II. Symptoms were mostly correlated with abdominal presentation; 15 out of 29 patients with abdominal prevalent disease had symptoms

Table 2. Presenting morphologic findings of 64 patients, and immunologic findings of 48 patients with LB. A significant statistical correlation was seen between Mediastinal and Convoluted cell type (P = 0.013) *or T phenotype* (P = 0.0011), *between abdominal involvement and "Burkitt" cell type* (P = 0.017) *or B phenotype* (P = 0.00042), *and between superficial node prevalent involvement and non B–non T phenotype* (P = 0.00024)

	Mediastinal 14		Abdominal 29		Superficial Node 21		Total	
Histology:								
Convoluted	8	58%	5	17%	5	24%	18	28%
Unclassified	3	21%	5	17%	10	48%	18	28%
Burkitt like	3	21%	19	66%	6	28%	28	44%
Immunology:								
B	1	10%	18	78%	6	40%	25	39%
T	8	80%	4	18%	/		12	19%
Non B–Non T	1	10%	1	4%	9	60%	11	17%

Table 3. Presenting clinical and hematological manifestations of 64 patients with lymphoblastic lymphoma (LB)

	Type of Presentation			
No. of patients	Mediastinal 14 (21.9%)	Abdominal 29 (45.3%)	Superficial Node 21 (32.8%)	Total 64
Mean age (yr)	30.7	41.4	40.0	38.0
Sex M	11 79%	23 79.3%	12 57.1%	46 71.8%
F	3 21%	6 20.7%	9 42.9%	18 29.2%
Symptoms A	12 85.7%	15 51.7%	16 76.2%	43 67.2%
B	2 14.3%	14 48.3%	5 29.8%	21 32.8%
Stage I	1 7.1%	2 6.8%	2 9.5%	5 7.8%
II	2 14.3%	4 13.7%	2 9.5%	8 12.5%
III	2 14.3%	3 10.3%	5 23.8%	10 15.6%
IV	9 64.2%	20 68.9%	12 57.1%	41 64%
Bulky Yes	9 64.2%	19 65.5%	7 33.3%	35 54.7%
No	5 35.8%	10 34.5%	14 66.7%	29 45.3%
Bone marrow Yes	8 57%	14 48.2%	10 47.6%	32 50%
involvement: No	6 43%	15 51.8%	11 52.4%	32 50%
Blood involvement:				
At diagnosis	3 21.4%	7 24.1%	4 19%	14 21.8%
During the course	4 28.6%	2 6.9%	3 14.3%	9 14%
CNS involvement:				
At diagnosis	1 14.3%	3 10.3%	1 4.7%	5 7.8%
During the course	3 21%	7 24.1%	3 28.1%	13 20.3%

as compared with the lower proportion recognized in the other clinical presentations. Bulky disease was mostly associated to abdominal and mediastinal presentation with about 65% of these patients presenting it.

Treatment and response to therapy

Forty-two patients underwent "cyclic" therapy (CHOP or BACOP); 16 patients (38%) obtained a complete remission (CR) with a median duration of 24 months, eight patients still remain in CR 40–82 months after therapy. Nineteen patients showed a partial remission (PR) and nine patients showed progressive disease despite the therapy. Eighteen patients underwent LSA_2-L_2 treatment; nine of them (50%) obtained a CR with a median duration of 36 months. Five patients still remain in CR 16–48 + months after therapy. Four patients obtained a partial remission (PR) and five patients were unresponsive to treatment. Three patients underwent autologous BMT; all obtained a CR. One of them showed an early relapse 3 months after the transplant with bone marrow and CNS involvement and died 3 months later; two patients are in complete unmaintained remission 18 and 22 months respectively after the transplant. One patient underwent allogeneic BMT; he still remains in CR 27 months after the transplant. No significant differences in remission rate were recorded among the different clinical presentations. Response to therapy was correlated only with the stage ($P < 0.005$) with a better remission rate of patients in stage I–II (77%) than patients in stage III–IV (35%).

Survival and prognostic analysis (Table 4)

The median survival of the whole group of patients was 12 months (Fig. 1). Forty-six patients (72%) died; nine patients (14%) survived longer than 36 months. A significantly better survival was recognized in patients without symptoms, patients with localized disease, (Fig. 2) patients without bulky disease, patients without bone marrow involvement, and in those achieving a CR. Other parameters such as age, sex, CNS involvement and leukemic manifestation were of borderline significance. The type of clinical presentation, the histology, the immunology and the type of therapy were not statistically significant. Since the number of patients who underwent BMT was small, no attempt was made to compare their survival with that of patients who did not have bone marrow transplantation.

The most important factor affecting prognosis was the response to therapy (Fig. 3). The median survival of the 28 patients who experienced CR was 34.5 months as compared to 9 months for patients who obtained only PR or 3 months for those who did not respond to therapy. A multivariate regression analysis showed the response to therapy as being the only covariate affecting survival. However a second analysis performed

Table 4. Prognostic univariate analysis according to parameters tested on 64 patients with LB

Parameters	Variables	Median survival (months)	*P* value
Sex	M	11	0.1
	F	24	
Age (median)	> 38 yr	10	0.1
	< 38 yr	15	
Clinical presentation	Abdominal	9	0.4
	mediastinal	15	
	Superficial node	22	
Symptoms	A	18	0.025
	B	7.5	
Stage	I	82	0.0005
	II	35	
	III	15	
	IV	9	
Bulky	Yes	9	0.025
	No	23	
Bone marrow involvement	Yes	10	0.025
	No	23.5	
Blood involvement	Yes	9	0.1
	No	15	
CNS involvement	Yes	5	0.1
	No	14	
Histology	Convoluted	11.5	
	Unclassified	23.5	0.2
	"Burkitt" like	9	
Immunology	B	9	
	T	12	0.2
	Non T–Non B	23	
Therapy	Conventional	12	0.2
	Intensive	7.5	
Response	Complete remission (CR)	34.5	
	Partial remission (PR)	9	0.0001
	No response (NR)	3	

taking into account the stage symptoms, bulky disease and bone marrow involvement showed the stage as being the most important factor affecting prognosis ($P < 0.005$).

DISCUSSION

Among high grade malignant lymphomas, lymphoblastic type (LB) reflects some distinct aspects.

As would be expected [4–10] we found a high incidence of bone marrow, blood, and CNS involvement, and we were not surprised to find as good prognostic features the absence of symptoms, localized disease, absence of bulky disease and the achievement of complete remission after treatment. However, despite the predictability of these observations two factors of considerable interest emerge: (1) the observation of heterogeneous presentation of the disease, and (2) the correlation between the type of clinical presentation and histologic/immunologic features.

The first point is firmly documented by the recognition of three clinical patterns which reflect important differences in the origin of the disease. In fact the prevalent mediastinal lymphoma implies a thymic origin of the disease; the abdominal masses probably arise from intestinal lymphoid tissue and sometimes implies an isolated intestinal mass. Prevalent superficial node disease suggests lymphoblast proliferation from the lymph nodes. This heterogeneous presentation of LB is associated with some differences in the distribution of the parameters tested. In fact younger patients are more commonly associated to mediastinal disease; patients with symptoms to abdominal disease and patients with localized stage (Stage I, II, III) to

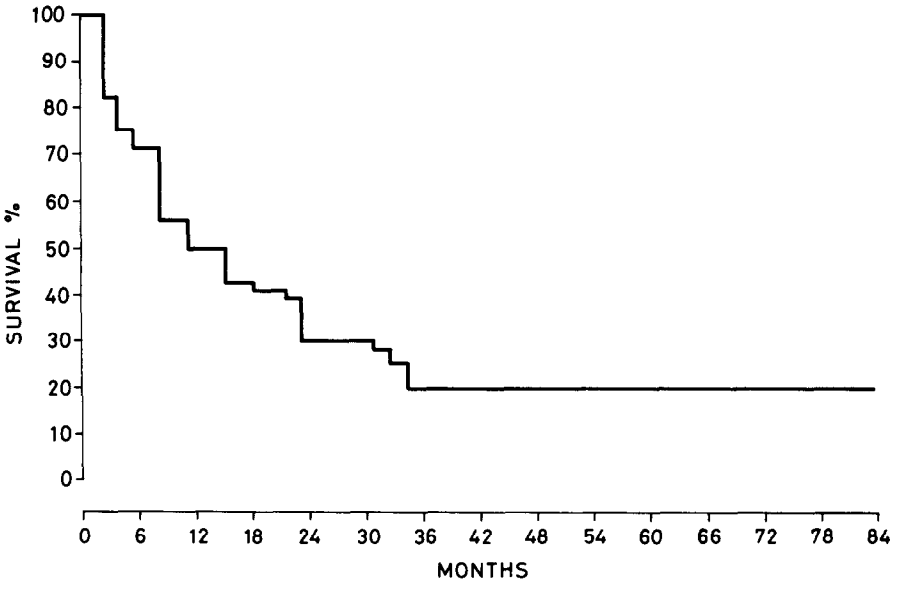

Fig. 1. Survival curve of 64 patients with lymphoblastic lymphoma (LB).

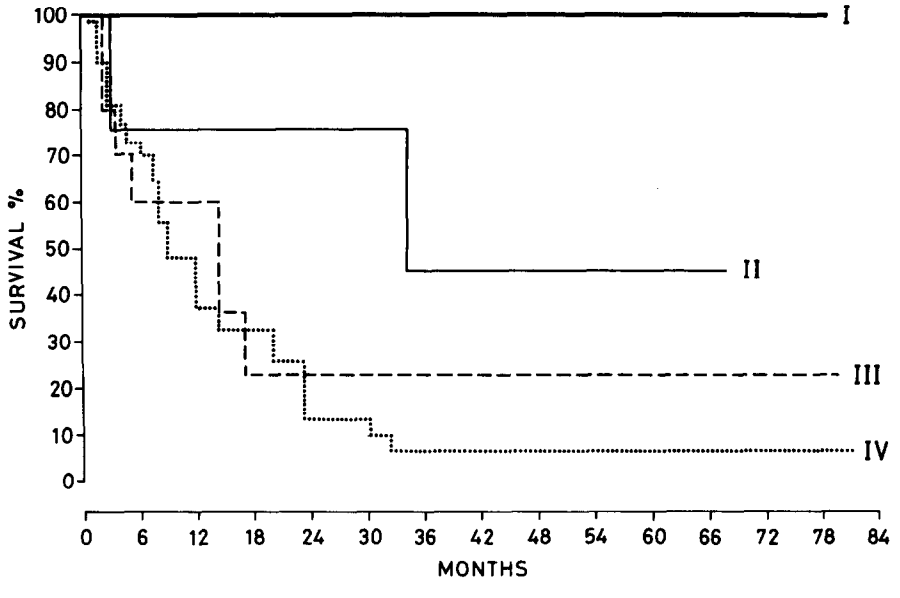

Fig. 2. Survival curves according to stage of the disease ($P < 0.0005$).

lymph-node prevalent disease. Unfortunately the different presentations showed no difference in prognosis and it is difficult to speculate on the therapeutic management of such different patients. However, the observation that patients with very limited disease in one or two sites have a good prognosis, and conversely, that patients with more disseminated disease have a poor outcome whatever protocol is employed, suggests to us that more aggressive therapeutic programs than those we generally employed should be explored. Autologous or allogeneic bone marrow transplantation following high dose therapy could be considered as alternative treatment for the latter group of patients. Since the number of patients who underwent this therapeutic approach is too small, it is difficult to make a firm conclusion.

The second interesting point is the peculiar distribution of histological and immunological features. Our study clearly demonstrated a significant correlation between prevalent mediastinal disease with convoluted cell type and T phenotype, between abdominal prevalent disease with "Burkitt" like cell type and B phenotype, and between

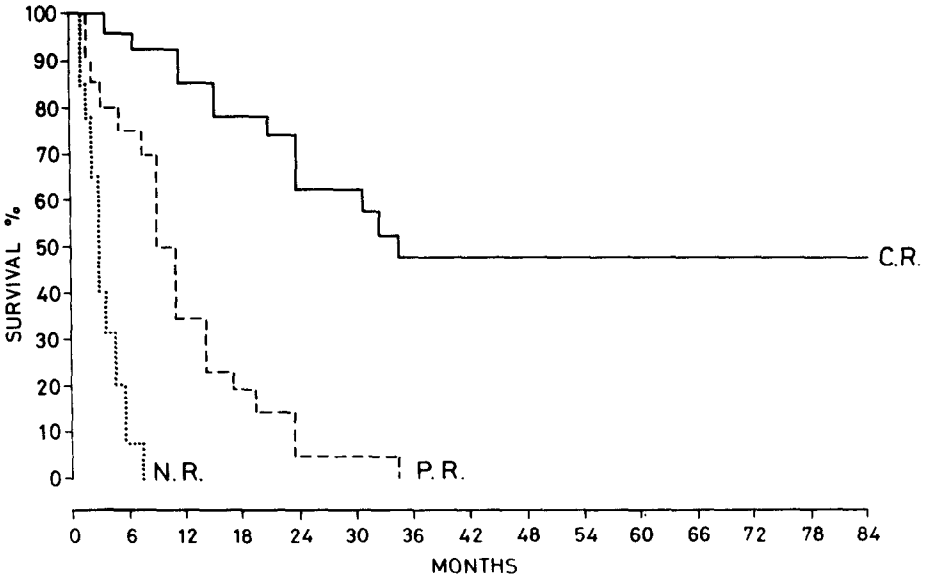

Fig. 3. Survival according to response to therapy. The median survival was 34.5, 9 *and* 3 *months for complete responders (CR), partial responders (PR) and non-responders (NR) respectively* ($P < 0.0001$).

superficial node prevalent disease with undifferentiated cell type and non B–non T phenotype. A similar correlation has also been clearly reported in children [9], in adult patients the correlation between T phenotype and mediastinal involvement is well known [22]. The correlation between B phenotype and abdominal presentation has been reported [38, 39]. We think that these findings could perhaps be of great importance in their clinical applications. First, the discovery of a number of T or B monoclonal cells in the marrow of patients with isolated mediastinal or abdominal mass respectively has a diagnostic relevance for lymphoma; in this case a more careful morphological analysis and a second bone biopsy could provide a diagnosis without the need for surgical operation. Second, hidden foci or minimal residual disease after first line therapy in patients programmed for autologous bone marrow transplantation should be checked properly by using the anti-T monoclonal antibodies in patients with mediastinal disease, or all the techniques available for the discovery of B monoclonal lymphoid cells in patients with abdominal disease. Finally, we do not yet know whether these techniques, as well as being of use in purging the harvested marrow of these patients, could also be used in the therapy of minimal residual disease after first line therapy.

Obviously these considerations fall well short of proposing a standardized clinical, histological and immunological model of LB; but they do reflect the need for a wider and more homogenous analysis than what has been reported hitherto, in order to improve the approach to the disease.

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