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The Value of Sequential Bone Marrow Biopsy and Laparotomy and Splenectomy in a Series of 200 Consecutive Untreated Patients with Non-Hodgkin's Lymphoma*

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Abstract—*The information derived from sequential routine bone marrow biopsies and exploratory laparotomy with splenectomy in 200 consecutive untreated protocol patients with malignant lymphomata other than Hodgkin's disease is reviewed.*

Of 114 patients with nodular lymphomata, 64% had a change of stage after these diagnostic procedures, almost all to more advanced stages, usually as a result of bone marrow biopsy. Of 86 patients with diffuse lymphomata, 29% changed stage, one-third of them to a lower stage. The correlation of pathological stages to clinical stages is presented for the major subgroups of the Rappaport classification.

Bone marrow biopsy demonstrates that 76% of patients with nodular lymphocytic poorly differentiated (NLPD) lymphoma have disseminated disease at the time of diagnosis. In only 13% of patients with diffuse histiocytic (DH) lymphoma is the bone marrow involved at the time of diagnosis. The different natural history of these two major histological subgroups is emphasized.

INTRODUCTION

In a previous report the Stanford experience with exploratory laparotomy and splenectomy for diagnostic and staging purposes in 127 consecutive untreated patients with non-Hodgkin's lymphomata was analysed [1]. In another publication Rosenberg reported the bone marrow involvement in a group of 109 patients with non-Hodgkin's lymphoma [2].

In this study we have extended our data to the first 200 consecutive untreated patients explored at the time of diagnosis by the same prospective procedures. The aim of this study is to get a better knowledge of the natural history of the non-Hodgkin's lymphomata, specially the extension of the disease at the time of diagnosis correlated to the Rappaport classification and to confirm or disprove the previous results about the incidence of bone marrow involvement of patients with non-Hodgkin's lymphomata at the time of diagnosis.

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MATERIALS AND METHODS

Patient selection

A consecutive series of 200 previously untreated patients who were part of a prospective therapeutic trial which was initiated in July, 1971, was studied. The selection of patients, criteria for eligibility for protocol study, preoperative studies and laparotomy techniques have been described in detail elsewhere [3–5].

In summary, the following criteria were used: (1) diagnostic biopsy was reviewed by the Stanford Division of Surgical Pathology, confirmed as malignant lymphoma other than Hodgkin's disease and classified according to

the Rappaport classification [6]; (2) patients were previously untreated; (3) patient lived within 300 miles of the Stanford Medical Center; (4) age between 10 and 70 yr inclusive; (5) patient and referring physician agreed to entry into randomized studies after being carefully informed about the investigative nature of the diagnostic and therapeutic programs; (6) patient did not have the clinicopathological diagnosis of chronic lymphocytic leukemia based upon previously defined criteria [7]; there existed no previous or concurrent medical condition which would seriously compromise the patient's ability to withstand the diagnostic and therapeutic program planned or the interpretation of the results of the studies.

The preoperative evaluation included bilateral pedal lymphography and needle biopsy of the bone marrow, in addition to other and routine studies described elsewhere [4, 8].

The surgical staging procedures included abdominal exploration, splenectomy, wedge and needle biopsies of the liver, selected paraaortic and mesenteric lymph node biopsies, open iliac crest bone marrow biopsy and oophoropexy, if indicated [5]. Metallic clips were used to mark the splenic vascular pedicle and all lymph node biopsy sites.

Of the 200 patients, 131 underwent exploratory laparotomy; 116 performed at Stanford Medical Centre and 15 at an outside hospital. In 69 patients, laparotomy was not performed because of the demonstration of bone marrow involvement. In 18 additional cases, bone marrow involvement was detected by open biopsy at the time of laparotomy. In eight patients in good general condition with positive needle biopsy of the bone marrow, laparotomy with splenectomy was performed for investigative purposes with the patient's informed consent. Thereafter, exploratory laparotomy was carried out only in patients who had prior negative or equivocal needle biopsy of the bone marrow.

The histological subgroups used were those of the Rappaport classification, as shown in Table 1. The usual abbreviations for the subgroups are also shown.

Tests of significance were done using the chi-square test with the Yates correction when indicated [9]. A simultaneous test for multiple comparisons on categorical data has been used [10] for the analysis of bone marrow involvement in the different histological subtypes.

RESULTS

The histological subgroups of the 200 consecutive untreated patients are shown in Table 1. In 9 cases, [5 nodular histiocytic (NH), 1 nodular mixed (NM), 1 NLPD and 2 DH], mixed or composite histological appearances were noted. Though this situation creates unanswered classification and management problems, for the purposes of this review, that appearance which seemed to predominate was used for analysis. In this series, the nodular patterns (114 cases) predominate over the diffuse patterns (86 cases). The largest subgroup is the NLPD type with 72 cases (36%) followed by DH with 56 cases (28%) and NM with 30 cases (15%). These three

Table 1. *Non-Hodgkin's lymphomata. Histopathological classification of* 200 *consecutive protocol patients*

Nodular			Diffuse		
	No. of cases			No. of cases	
NLWD	—	Nodular lymphocytic well differentiated	DLWD	6	Diffuse lymphocytic well differentiated
NLPD	72	Nodular lymphocytic poorly differentiated	DLPD	'13	Diffuse lymphocytic poorly differentiated
NM	30	Nodular mixed histiocytic–lymphocytic	DM	9	Diffuse mixed histiocytic–lymphocytic
NH	12	Nodular histiocytic	DH	56	Diffuse histiocytic
			DU	2	Diffuse undifferentiated
Total	114		Total	86	

Table 2. Non-Hodgkin's lymphomata. Bone marrow involvement of 200 consecutive patients

	NLPD	NM	NH	DLWD	DLPD	DM	DH	DU	Nodular patterns	Diffuse patterns	Total non-Hodgkin's lymphomata
No.	72	30	12	6	13	9	56	2	114	86	200
BM+	55	11	2	6	2	7	7	—	68	22	90
%	76*	36	17†	100*	15†	78*	13†	—	60.	24	45

* and † form two homogeneous populations ($P<0.05$). See statistical analysis [10].

Table 3. Non-Hodgkin's lymphomata. Correlation between bone marrow involvement and clinical stage

Clinical stage	NLPD		NM		NH		DLWD		DLPD		DM		DH		DU		Nodular patterns		Diffuse patterns		Total non-Hodgkin's lymphomata	
	BM+	BM−	BM+	BM−	BM+	BM−	BM+	BM−	BM+	BM−	BM+	BM−	BM+	BM−	BM+	BM−	BM+	BM−	BM+	BM−	BM+	BM−
I	2	1	1	2	—	—	—	—	—	2	—	—	—	10	—	1	3	3	—	13	3	16
II	2	7	1	6	—	2	—	—	—	4	—	1	—	14	—	—	3	15	—	19	3	34
III	45	9	7	11	1	8	4	—	2	2	4	1	5	16	—	—	53	28	15	19	68	47
IV	6	—	2	—	1	—	2	—	—	3	3	—	2	9	—	1	9	—	7	13	16	13
Total	55	17	11	19	2	10	6	—	2	11	7	2	7	49	—	2	68	46	22	64	90	110

subgroups comprise almost 80% of the patients.

Sex distribution

There were 111 males and 89 females in the group with an overall M:F ratio of 1.2:1. The sex distribution is virtually equal in patients with nodular patterns (56 males vs 58 females), but shows a male predominance in those with diffuse patterns in a ratio of 1.7:1.

Age distribution

The age distribution of patients is different for the various histologic subgroups. Patients in the NLPD subgroup tended to be older with 61 of the patients (85%) over 40 yr of age, the youngest being 28. The DH subgroup shows a much wider distribution with 20 patients (35%) younger than 40 yr and 7 patients (12.5%) of less than 20 yr. A similar distribution is shown in diffuse lymphocytic poorly differentiated (DLPD) lymphoma with 3 of 13 patients under the age of 20 yr. No patient with a nodular pattern was younger than 25 yr. There is no correlation between age and clinical or pathological stage at the time of diagnosis.

Bone marrow involvement

Table 2 shows the incidence of bone marrow involvement among the various histological subgroups. In 90 of 200 patients, bone marrow involvement was identified, an overall incidence of 45%. There is a striking difference of the incidence of bone marrow involvement in the nodular subtypes, 68 of 114 patients (60%) as compared to those with diffuse patterns, 22 of 86 patients (24%). The difference is even more striking when the two main histological subtypes are compared. The NLPD group shows bone marrow involvement at the time of diagnosis in 55 of 72 patients (76%) while DH patients have bone marrow involvement in only 7 of 56 patients (13%). A low incidence is also found in those patients with DLPD, only 2 of 13 patients (15%) were affected at the time of diagnosis. On the contrary, diffuse lymphocytic well differentiated (DLWD) and diffuse mixed (DM) groups show a high bone marrow incidence, DLWD 6 of 6 patients (100%) and DM 7 of 9 patients (77%). In the nodular types, nodular histiocytic (NH) behaves like DH with only 2 of 12 patients (16%) with bone marrow involvement and the nodular mixed (NM) subtype presents an intermediate degree of bone marrow involvement, 11 of 30 patients (36%).

Bone marrow involvement is correlated with the clinical stage of disease for the different histological subtypes. In the NLPD subgroup, 51 of 60 cases (85%) of those with clinical stages III and IV had bone marrow involvement. In NM, 9 of 20 cases (45%) with clinical stage III or IV disease have bone marrow involvement. In contrast, in the DH group of 32 patients with clinical stages III and IV disease, only 7, or 22%, have bone marrow tumor. Bone marrow involvement is uncommon in the setting of clinical stages I and II [six of 56 (11%) of all histologic subtypes] with the highest incidence in patients with NLPD [4 of 12 (33%)] (Table 3).

Bone marrow aspirate showed lymphoma in only one patient with NLPD. In this subtype, 47 instances of bone marrow involvement were diagnosed by needle biopsy and only 8 additional cases were detected by open biopsy. In the NM type, bone marrow involvement was diagnosed in eight cases by needle biopsy and in another three cases by open biopsy. In the DH type, three cases were detected by needle biopsy and four by open biopsy. Considering all subtypes together, of the 90 patients with bone marrow involvement, 70 were diagnosed by needle biopsy and 20 by open biopsy, 18 of them at the time of laparotomy.

Changes of stage

Table 4 compares the clinical stage of the entire group with the pathological stage determined by sequential bone marrow biopsy and laparotomy with splenectomy when indicated. About half of the cases, 98 out of 200 (49%) had a change of stage; 88 (44%) to a more advanced stage and 10 (5%) to a lower stage. The majority of those with a higher stage was as a result of finding bone marrow involvement. This occurred in 73 patients, 8 of whom also showed liver involvement when the laparotomy was performed. In 6 cases, the change was due to liver involvement alone. In the other 9 cases, the change was due to the finding of unsuspected abdominal involvement. Of the 10 cases whose clinical stage was reduced, 8 were as a result of an abnormal lymphogram and palpable spleens in two patients which could not be confirmed as due to disease after laparotomy and splenectomy.

Table 4. *Non-Hodgkin's lymphomata. Two hundred consecutive untreated patients. Changes of stage*

	Pathological stage				
Clinical stage	I	II	III	IV	Total
I	**15**	1	—	3	19
II	—	**26**	8	3	37
III	4	5	**33**	73	115
IV	—	1	—	**28**	29
Total	19	33	41	107	200

Changed 98/200 (49%); upward 88/200 (44%), downward 10/200 (5%).

Table 5. *Changes of stage. Nodular patterns*, 114 *patients*

	Pathological stage				
Clinical stage	I	II	III	IV	Total
I	**3**	—	—	3	6
II	—	**7**	8	3	18
III	2	1	**22**	56	81
IV	—	—	—	**9**	9
Total	5	8	30	71	114

Changed 73/114 (64%); upward 70/114 (61%), downward 3/114 (3%).

Table 6. *Changes of stage. Diffuse patterns*, 86 *patients*

	Pathological stage				
Clinical stage	I	II	III	IV	Total
I	**12**	1	—	—	13
II	—	**19**	—	—	19
III	2	4	**11**	17	34
IV	—	1	—	**19**	20
Total	14	25	11	36	86

Changed 25/86 (29%); upward 18/86 (21%), downward 7/86 (8%).

Table 7. *Changes of stage. NLPD*, 72 *patients*

	Pathological stage				
Clinical stage	I	II	III	IV	Total
I	**1**	—	—	2	3
II	—	**4**	3	2	9
III	—	—	**7**	47	54
IV	—	—	—	**6**	6
Total	1	4	10	57	72

Changed 55/72 (76%) all upward.

Table 8. *Changes of stage. NM*, 30 *patients*

	Pathological stage				
Clinical stage	I	II	III	IV	Total
I	**2**	—	—	1	3
II	—	**1**	5	1	7
III	1	—	**10**	7	18
IV	—	—	—	**2**	2
Total	3	1	15	11	30

Changed 15/30 (50%); upward 14/30 (46%), downward 1/30 (4%).

Table 9. *Changes of stage. DH*, 56 *patients*

	Pathological stage				
Clinical stage	I	II	III	IV	Total
I	**9**	1	—	—	10
II	—	**14**	—	—	14
III	1	3	**11**	6	21
IV	—	1	—	**10**	11
Total	10	19	11	16	56

Changed 12/56 (21%); upward 7/56 (13%); downward 5/56 (9%).

Table 10. *Non-Hodgkin's lymphomata. Correlation between spleen weight and spleen and liver involvement*

Spleen weight	Nodular patterns			Diffuse patterns			Non-Hodgkin's lymphomata		
	No	S+	L+	No	S+	L+	No	S+	L+
0–200 g	40	16	4	34	5	1	74	21	5
201–400 g	9	6	1	10	3	1	19	9	2
400 g	6	6	3	7	7	5	13	13	8
Total	55	28	8	51	15	7	106	43	15

Table 11. *Non-Hodkgin's lymphomata. Lymphangiographic accuracy*

	Lymphangiographic interpretation					
	+		Equiv.		−	
No.	65		13		32	
Pathologic findings in para-aortic nodes	+	−	+	−	+	−
	53	12	1	12	5	27
% Accuracy	81%				84%	

Tables 5 and 6 show the changes of stage in the nodular and diffuse patterns. The nodular subtypes demonstrate a higher incidence of upward changes, 70 of 114 (61%) because of the higher incidence of bone marrow involvement in this group. In contrast, the diffuse patterns have a lower frequency of change of stage, only 25 of 86 cases (29%). Almost a third changed to a lower stage.

Tables 7, 8 and 9 show the changes of stage in the three major histological subtypes.

Spleen and liver involvement

Of 27 patients with bone marrow involvement who had an exploratory laparotomy, 19 had spleen involvement (70%) and 12 liver involvement (44%). In contrast, of 92 patients without demonstrated bone marrow involvement, 28 had spleen involvement (30%) and only seven had liver involvement (7.6%).

In only one patient with lymphoma of the liver was the spleen uninvolved at laparotomy. In all other cases, when the liver was involved, the spleen was also involved.

The correlation of splenic weight to histological splenic involvement is shown in Table 10. The larger the spleen, the more likely it was to be involved with lymphoma. However, of 74 spleens weighing less than 200 g, 21 (28%) had occult lymphomatous involvement. The weight range of uninvolved spleens was 40–400 g. With the exception of one patient with DH whose uninvolved spleen weighed 400 g, all other negative spleens weighed less than 260 g. The range of involved spleens was 75–2400 g. All spleens over 400 g were involved.

Liver involvement was demonstrated in 19 of 119 cases in which the liver biopsy was performed, an incidence of 16%. However, liver biopsies were not obtained in the majority of patients who had demonstrated bone marrow involvement by needle biopsy.

Lymphogram (LAG) reliability

The accuracy of lower extremity lymphogram within the limitations of surgical sampling of the retroperitoneal, para-aortic and iliac lymph nodes is shown in Table 11. Lymphography was accurate in more than 80% of the cases in which a laparotomy was performed.

Mesenteric and para-aortic node involvement

Mesenteric node involvement was pathologically identified in 55 (45%) patients who underwent laparotomy. This occurred in 37 (58%) of 63 of those patients with nodular histologies and in 18 (31%) of 58 patients with diffuse histologies. Para-aortic and/or iliac node involvement was identified in 61 (50%) of 121 patients, 41 (65%) of 63 with nodular patterns and 20 (34%) of 58 with diffuse patterns.

Bone marrow involvement and laboratory data

The peripheral blood counts were poor indicators of bone marrow involvement. In the nodular patterns, anemia, leukopenia or thrombocytopenia were found in four patients with bone marrow involvement and in two patients without bone marrow involvement. An absolute lymphocytosis was observed in only one patient with bone marrow involvement. In the diffuse patterns, anemia and leukopenia were found in two patients with bone marrow involvement and in six patients without bone marrow involvement. Borderline lymphocytosis was found in one patient with DLPD with bone marrow involvement and in five patients with DH without bone marrow involvement.

The serum alkaline phosphatase level was determined in all 90 patients with bone marrow involvement and did not predict this site of disease, as seen in Table 12.

Table 12. Non-Hodgkin's lymphomata. Correlation between serum alkaline phosphatase levels and bone marrow involvement

		Serum alkaline phosphatase		
	No.	Elevated*	Borderline	Normal
BM−	110	8%	16%	76%
BM+	90	4%	9%	87%

*Greater than 150% of the upper limit of normal.

Special presentation patterns

Certain clinical and pathologic differences are apparent in the two main subgroups of patients. Patients with NLPD are usually older than 40 yr (85% of the patients) and in the majority of cases (67 of 72 patients), the disease involves peripheral lymph node areas at the time of diagnosis. In 13 patients, there was radiological evidence of mediastinal adenopathy, but never massive and always associated with peripheral lymph node involvement. In 4 patients, abdominal masses were detected by palpation, all associated with peripheral adenopathy. In only one patient was the small bowel involved. Two patients, one with a massive splenomegaly and another with a pelvic mass, showed no peripheral adenopathy.

In contrast, patients with DH present in a younger age group. Peripheral lymphadenopathy was present at diagnosis in 31 (55%) of 56 patients. In 4 young patients the disease presented as a massive mediastinal mass without peripheral adenopathy and in 2 other patients the lung was involved. In 3 patients the disease appeared to arise in the stomach and in 2, in the ileum, all of whom had no peripheral node involvement. In 6 patients the disease presented clinically as an abdominal mass and in one as a pelvic mass. In 2 patients, there were lytic bone lesions in skull and humerus without peripheral adenopathy.

Statistical analysis

The statistical analysis of the bone marrow involvement in the different histological subgroups with the simultaneous test for multiple comparisons on categorical data [10] shows clearly two homogeneous populations: NLPD–DLWD–DM and DH–DLPD–NH ($P<0.05$).

When we compare the two main histological subgroups NLPD and DH, we find many statistically significant differences by the chi-square test. Some of these statistically significant differences are: the bone marrow involvement ($P=0.001$); changes of stage ($P<0.001$); pathological stages I and II vs pathological stages III and IV at the time of diagnosis ($P<0.001$); spleen and liver involvement ($P<0.05$) and mesenteric and paraaortic node involvement ($P<0.05$). Evidently, NLPD and DH form two extreme opposite nosological entities in the spectrum of non-Hodgkin's lymphomata.

DISCUSSION

The diagnostic procedures of bone marrow biopsy, laparotomy and splenectomy have shown us striking differences in particular histologic subgroups which are probably related to a different natural history of these subgroups.

NLPD appears to be a particular homogeneous subgroup. Eighty-six per cent of the patients were older than 40 yr. The male:female (M:F) ratio was almost equal. Seventy-six per cent of the patients of this subgroup showed bone marrow involvement at the time of diagnosis. Of the 55 NLPD patients without bone marrow involvement at (93%) had widespread disease of clinical stages III and IV extent and only 4 (7%) had clinical stages I and II. In contrast, of 17 patients without bone marrow involvement at the time of diagnosis, 9 (53%) had clinical stage III disease and 8 (47%) had clinical stages I and II.

Laparotomy was not routinely performed in NLPD patients because of the high frequency of bone marrow involvement. But in 12 patients with bone marrow involvement in which laparotomy was performed, the spleen was involved in 9 of 11 patients (82%) (one spleen had been previously removed because of trauma), and the liver was involved in 8 of 12 patients (66%). In 15 NLPD patients without bone marrow involvement, the spleen was affected in 6 of 15 cases (40%) and the liver in 2 (13%).

In 93% of NLPD patients, the disease presented with peripheral adenopathy at the time of diagnosis. Since the older patients have more difficulty with surgery and NLPD patients, even with widespread disease, have relatively indolent courses, it should be emphasized that adequate bone marrow biopsy be obtained with repeated needle or open biopsies to avoid the laparotomy in these patients, whenever possible.

In NLPD patients, changes from clinical to pathological stage occurred in 52 of 72 patients (76%), all of them because of bone marrow

Table 13. Non-Hodgkin's lymphomata. Bone marrow involvement in the present study and in other series in which the Rappaport Classification was used

	Jones *et al.* [11]	Dick *et al.* [12]	Rosenberg [2]*	Stein *et al.* [13]	Chabner *et al.* [14]	Castellani *et al.* [15]	Present study
	(%)	(%)	(%)	(%)	(%)	(%)	(%)
NLPD	30	57	85	59	40	10	76
NM	15	—	31	0	46	14	36
NH	—	—	—	—	14	—	17
DLWD	—	100	—	100	100	67	100
DLPD	29	27	30	61	54	33	15
DM	21	—	60	—	33	20	78
DH	5	17	9	5	15	4	13
No. of cases	218	108	109	121	170	119	200

*Excludes patients also reported retrospectively by Jones *et al.* [11].

involvement. Thus, at diagnosis, 67 (93%) belonged to pathological stages III and IV.

DH, in spite of its diffuse pattern, behaves differently and appears disseminated in only about one-fourth of the patients at the time of diagnosis. DH shows 35% of the patients younger than 40 yr. The M:F ratio is 1.6:1. The bone marrow was involved at the time of diagnosis in only 13% of these patients. Of 56 DH patients, only 12 (21%) changed stage, 7 (13%) upwards and 5 (9%) downwards. DH often presents in young patients with a massive mediastinal or abdominal involvement and no peripheral adenopathy. It may be that some of these patients would be classified as having lymphoblastic or convoluted cell lymphoma, by current criteria [16], DH also affects the gastrointestinal tract more frequently than other subtypes.

Interestingly enough, NH behaves more in accordance with its cell type than like the other nodular types. Only 2 of 12 patients (17%) showed bone marrow involvement at the time of diagnosis. Four patients (30%) were younger than 40 yr and two-thirds of the patients belonged to a pathological stage II or III at the time of diagnosis, making this group more similar to the DH group than to the other nodular groups.

This study shows interesting differences between NLPD and NM. Only about one-third of the patients of the NM subgroup were classified as pathological stage IV and half had pathological stage III. There was no case of liver involvement among the 22 laparotomies done in this group. This was the only subgroup with no liver involvement at the time of diagnosis.

The DLPD group shows a low incidence of bone marrow involvement in contrast to its nodular counterpart. Only 2 of 13 patients (15%) had bone marrow disease. Half of the patients were classified as pathological stages I and II and 3 patients (23%) were younger than 20 yr. In contrast, DLWD and DM present high incidences of bone marrow involvement, 100 and 78% respectively, showing a greater tendency to dissemination.

The distribution of histological subgroups in our series is not comparable with other published series [12, 13, 15] that show a great predominance of the diffuse patterns over the nodular patterns. Only the series more recently published by Nathwani *et al.* [17] and by Chabner *et al.* [14] have a similar distribution with two subgroups emerging also with particular characteristics, the NLPD and DH groups. Our results agree also with these latter

authors as they comment that rigorous staging placed virtually all patients with nodular lymphoma in advanced categories of disease (stages III or IV) and defined a substantial number of patients with limited disease only in the histiocytic lymphoma group. Of their DH patients, 30% had stage I or II and 15% had bone marrow involvement at the time of diagnosis. This is in contrast with a previous publication [18] where the diffuse lymphomas showed a high degree of abdominal nodes and liver involvement. Castellino *et al.* [15] also report that patients with DH appear to be the subgroup with the lowest incidence of both liver (13%) and bone marrow (4%) infiltration.

The incidence of bone marrow involvement at the time of diagnosis confirms the preliminary data obtained by Rosenberg [2]. The results show clearly that the overall data in non-Hodgkin's lymphomata (45% with bone marrow involvement at the time of diagnosis) have, in themselves, no special meaning, while, when we split the data according to the histological subgroups, we find statistically significant differences: NLPD 76% with bone marrow involvement vs DH 13% at the time of diagnosis ($P<0.001$).

Our results are partially in agreement with other published series on the frequency of bone marrow involvement in non-Hodgkin's lymphomata. In Table 13, we show a summary of these results. There is a striking agreement of all series on the lower percentage of bone marrow involvement of DH patients at the time of diagnosis. Chabner *et al.* [14] also demonstrate a low incidence of bone marrow involvement in NH patients (14%) but their results in the NLPD and DLPD patients (40 and 50% respectively) are not in aggreement with our data. Dick *et al.* [12] series show a rather high incidence of bone marrow involvement in NLPD patients (56%) and a rather low incidence in DLPD patients (27%). This difference is even greater in our series. DLWD is a small subgroup of the non-Hodgkin's lymphomata with a well known very high incidence of bone marrow involvement in most of the published series.

The spleen weight roughly correlates with the spleen involvement. All spleens heavier than 400 g were involved. Between 200 and 400 g 47% were involved and under 200 g, one in four was involved, which means, as in Hodgkin's disease, that a nonpalpable spleen even of normal size might be affected. Except in one case of DH with an uninvolved spleen of 400 g, all negative spleens weighed less than 260 g which coincides with the data of Lotz *et al.* [18] in which all negative spleens weighed less than 270 g.

Our study shows the great frequency of mesenteric node involvement in non-Hodgkin's lymphoma as has been previously emphasized [1] in contrast to the low incidence in Hodgkin's disease [19]. In 45% of patients subjected to laparotomy, the mesenteric nodes were involved. Again the data are more significative when we look at the different histological subtypes. This occurred in 64% of the laparotomized NLPD patients and only in 31% of DH patients ($P<0.05$). This observation has important implications in the planning of radiation therapy with a curative intent [20].

Only one patient with NLPD presented with a normal spleen and an involved liver. In all other cases when the liver was affected, the spleen was also affected. Non-Hodgkin's lymphomas behave in this respect as Hodgkin's disease. This has also been confirmed by Lotz *et al.* [18]. Nevertheless, there are in the literature a few exceptions as reported by Castellani *et al.* [15] who found among 80 laparotomized patients four in whom a positive liver was not associated with splenic involvement. In a previous study, Chabner *et al.* [21] reported two DLPD patients from a total of 40 laparotomies with negative spleen and positive liver. Possibly in non-Hodgkin's lymphoma, these exceptions may be more frequent than in Hodgkin's disease.

Lymphography maintains a high level of accuracy in over 80% of the patients with non-Hodgkin's lymphoma. Some apparent false-positive cases may be due to surgical difficulties of sampling the appropriate nodes.

In contrast, neither the peripheral counts nor the serum alkaline phosphatase levels are of value in predicting the bone marrow involvement of the patients with non-Hodgkin's lymphoma.

The main purpose of our discussion is to make clear that the Rappaport classification appears to distinguish at least two clearly defined subgroups: NLPD and DH.

In our series, NLPD appears as a quite homogeneous group with a clear distribution in older people, equal M:F ratio, widespread dissemination to the peripheral nodes and involvement of the bone marrow in about 76% of the patients at the time of diagnosis. This might be due, as suggested by Dorfman [22], because the majority of the nodular lymphomas are produced by a monoclonal

proliferation of B cells. Lukes and Collins [23] stated that the small cleaved cells exhibit little cellular cohesion, may be found in the peripheral blood as cleaved nucleated cells and account for the widespread "seeding" to the marrow, spleen and liver, possibly as a result of the normal "homing tendency" of B cells to these sites. Warnke and Levy [24] have recently published that the transformed cell of nodular lymphomata that gives rise to the malignant clone appears to be a migratory B cell with a tendency to home to the B cell domains of the lymphatic system, including the bone marrow. This suggestion may explain the high frequency of bone marrow infiltration of NLPD cases at presentation but does not explain why patients with NM and NH, also B-cell lymphomas, have a lower incidence of bone marrow involvement.

The DH group, especially the young population affected, represents another definite type of non-Hodgkin's lymphoma. The frequency of mediastinal involvement suggests that some of these cases may be examples of the Sternberg sarcoma of the convoluted T-cell type, also called malignant lymphoma, lymphoblastic type, by Rappaport [16] which are associated with a high incidence of development of lymphoblastic leukemia and meningeal involvement. According to Dorfman and Kim [19], however, these lymphomata are more often of the DLPD type in the original Rappaport system. On the other hand, at least at diagnosis, we could not find an early tendency to develop leukemia in the cases of this group.

The frequency of possible primary digestive involvement is another characteristic of some juvenile and adult DH cases. These "histiocytes" might be, according to Lukes and Collins [23], the large cleaved follicular center cells, the large non-cleaved follicular center cells and the socalled immunoblast of B or less frequently T origin as well as "true" histiocytic cells. Chabner *et al.* [14] found in the DLPD group, an increased frequency of extranodular tumors originating in gastrointestinal sites, bone and skin. Perhaps some of our DH cases or some of their DLPD cases were borderline cases formed by large cleaved or large non-cleaved cells. Or perhaps, as we suggest from the study of our series, DH patients and DLPD patients belong to a "unique" group according to their similar bone marrow infiltration at the time of diagnosis (13 and 15%), half of the patients with localized disease (pathological stages I and II), and a younger population affected.

In a recent publication, Hausner *et al.* [25] described 30 patients of non-Hodgkin's lymphoma under 20 yr of age. There were 10 cases of lymphoblastic lymphoma (DLPD), none of them with convoluted nuclei and all with mediastinal mass, 10 Burkitt's lymphoma, 6 undifferentiated lymphoma and 4 with histiocytic lymphoma, with a great predominance of male patients.

We are not sure that all our 56 DH patients belong to the same nosological entity, but the low infiltration of bone marrow at diagnosis (13%), the limited spread of disease (52% pathological stages I and II), the lower frequency of liver (7%), spleen (21%) and mesenteric nodes (31%) involvement, the special tendency to affect primarily extranodal sites or produce mediastinal masses, the presentation of almost half of the patients without affecting the peripheral nodes, the age of distribution with a definite young group of patients, and the male predominance, allow us to suggest that there is possibly an underlying nosological entity that encompasses the majority of these cases. Chabner *et al.* [14] have also emphasized the unique clinical characteristics of this histological subgroup.

Although it has not been the purpose of this study, there are also clear differences between NLPD and DH cases in respect to their natural evolution and response to therapy. NLPD cases, despite widespread dissemination at the time of diagnosis, follow an indolent course and the results according to survival are similar with aggressive or less aggressive chemotherapy [26, 27]. In contrast, DH patients tend to progress rapidly to a fatal outcome unless complete remission is achieved with local radiation [28] and, in cases of advanced disease, there is a significant percentage of curable cases with intensive combination chemotherapy [29].

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