

Non-Hodgkin's Lymphomas in Leukemic Phase: Clinicopathologic Correlations (NCL)

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A leukemic phase occurred in 30 (14 percent) of 214 patients with non-Hodgkin's lymphoma. To determine the significance of peripheral blood involvement in each type of NHL, patients were subdivided according to a modified Rappaport classification. Each histologic subtype presented a homogeneous clinical picture which differed from that seen in other histologic subtypes. Of particular note was the recognition of two distinctive cytologic and clinical subtypes within the category of nodular lymphoma, poorly differentiated lymphocytic lymphoma (NPDL). In one subtype, the predominant cells had cytologic features akin to those of lymphoblasts. In these cases, although the interval to peripheral blood involvement was variable, the median leukemic survival was only two months. In contrast in conventional NPDL the median leukemic survival was 43+ months, and peripheral blood involvement did not appear to exert an independent effect on prognosis. In diffuse large cell lymphomas the median leukemic survival was 0.5 months, with peripheral blood involvement appearing as a terminal event associated with unresponsive disease in multiple sites. The recognition of adult lymphoblastic lymphoma as a clinicopathologic entity with a high risk of leukemic conversion, 100 percent in this study, is also confirmed.

The presence of malignant lymphoid cells in the peripheral blood is an infrequent but well appreciated manifestation of non-Hodgkin's lymphoma [1-3]. Early observers considered this phenomenon a lymphatic leukemia developing late in the course of a lymphosarcoma [4]. In 1937, Issacs [5] described the morphologic similarity between the circulating malignant cell and that in the lymphosarcomatous node, suggesting that the leukemic phase was a manifestation of the underlying disease. Although all but one of Issacs' cases became leukemic preterminally, Schwartz [6], and later Zacharski [7], reported that leukemia with these distinctive cells—lymphosarcoma cell leukemia (LSCL)—could be the presenting manifestation of lymphosarcoma. Schnitzer et al. [8], applying the classification of Gall and Rappaport concluded that LSCL was the leukemic phase of poorly differentiated lymphocytic lymphoma. Subsequent reports have established that leukemic phase may occur in other subtypes of non-Hodgkin's lymphoma [9-12].

Most previous descriptions of such a leukemic picture were written prior to the routine application of Rappaport's classification and prior to recent advances in the treatment of lymphoma which have produced gains in disease-free survival [13]. Our population with lymphoma has been carefully classified, staged and prospectively followed with

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TABLE I Clinical Features

	Nodular Lymphomas			Diffuse Lymphomas		
	Group I—NPDL	Group II—NPDL-B1	Group II—NLCL	DWDL	DLCL	DLBL
Cases (no)	5	5	1	6	4	9
Age (yr)						
Median	49	47	59	42	36	36
Range	40-57	39-55	59	29-65	12-65	2-65
Marrow involvement at diagnosis	4	1	1	6	1	4
Leukemic at diagnosis	3	0	1	5	0	4
Subsequent leukemic progression	2	5	0	1	4	5
Maximum white blood cell count ($\times 10^3/\text{mm}^3$) during leukemic phase						
Median	21	15	39	23	11	31
Range	7-31	7-208		11-92	7-17	8-120
Abnormal white blood cell count (%) during leukemic phase*						
Median	64	90	90	85	16	85
Range	46-87	61-95	...	50-100	13-32	14-95
Cerebrospinal fluid involvement	0	2	0	2	4	7
Total survival (mo)						
Median	54	54	21	42	10	13
Range	43-176	12-115	...	13-110	4-	3-45
Survival after onset of leukemic phase (mo)						
Median	43	2	21	37	0.5	4
Range	20-54	1-3	...	13-110	02-1	2-35

NOTE: Groups I + II = see text. NPDL = nodular poorly differentiated lymphocytic; NPDL-B1 = nodular poorly differentiated lymphocytic with blastic cytologic features; NLCL = nodular large cell, DWDL = diffuse well differentiated lymphocytic; DLCL = diffuse large cell; DLBL = diffuse lymphoblastic.

* Highest percentage of peripheral white blood cell differential composed of malignant cells.

current treatment protocols. Accordingly, we set out to assess and compare the pathologic and clinical features of leukemic involvement in the various types of non-Hodgkin's lymphoma.

MATERIALS AND METHODS

The clinical records of 214 consecutive, previously untreated patients with non-Hodgkin's lymphoma followed at the Medicine Branch of the National Cancer Institute between 1965 until 1977 were evaluated. Thirty patients (14 percent) who, at some point in their course, had repeated documentation of at least 10 percent malignant cells in the white blood cell differential, form the basis of this report.

All 30 patients had complete blood counts, peripheral smears, and bone marrow aspirates and biopsies as part of their initial evaluation. Complete blood counts and peripheral smears were obtained at each visit for all patients. Repeat bone marrow examinations were performed in 27 patients. The peripheral smears and the pathologic material from all diagnostic biopsies and recurrences were reviewed without knowledge of the patient's clinical course. Each patient was classified by the Rappaport system [14] with minor modifications [15].

The mitotic index per high powered field was determined on both primary and all subsequent lymph node biopsy specimens. This figure represents the average number of mitoses per high powered field in 20 consecutive high powered fields without regard to intra- or extranodal location. For nodular lymphomas, the degree of nodularity of the primary biopsy specimen was graded on a scale of 1 to 4. One plus indicated

vague, poorly demarcated nodularity; 4 indicated sharply defined distinct nodularity throughout the node.

In 16 of the 30 patients, neoplastic cells were obtained from either peripheral blood and/or lymph nodes or spleens for immunotyping. Suspensions of mononuclear cells were prepared by standardized, previously described methods [16]. Cells were characterized for surface immunoglobulins and rosette formation with erythrocytes coated with IgM antibody and complement (EAC), erythrocytes coated with IgG antibody (IgGEA) and unsensitized sheep erythrocytes (E) by previously described techniques [16,17]. In eight patients, terminal deoxynucleotidyl transferase (TdT) activity was assayed by methods previously reported [18]. Detailed results of the surface marker studies of these lymphomas are reported elsewhere [19]. Immunotypes were assigned based on these standard immunologic assays. B cell tumors had surface immunoglobulin and, in most cases, EAC receptors. T cell tumors were identified by their ability to form E rosettes. Tumors lacking B or T cell markers were termed "null."

All patients were staged pathologically as outlined by the Ann Arbor conference [20]. The initial treatment of the 30 patients consisted of cyclical combination chemotherapy (18 patients), single alkylating agents (four patients), total body irradiation (six patients) or involved field radiotherapy (two patients). The details of these regimens are described elsewhere [21-24].

Complete remission indicated disappearance of all evidence of disease ascertained by restaging one month after the cessation of therapy. The duration of the remission was calculated from the last day of treatment. Partial remission was defined

as 75 percent reduction or stabilization of disease on restaging. Survival was measured from the date of diagnosis.

RESULTS

Thirteen patients were in remission at the time of diagnosis; in 17, a leukemic phase developed during the clinical course. The median survival during the leukemic phase was 4.3 months (range 0.5 to 35 months). The median white blood cell count at the onset of the leukemic phase was $7,000/\text{mm}^3$ (range 2,000 to $20,000/\text{mm}^3$). The median percentage of malignant cells in the white blood cell differential was 64 percent (range 46 to 95 percent).

The histologic subtypes of the leukemic manifestation were as follows:

Nodular Lymphoma. The leukemic manifestation was classified as nodular lymphoma in 10 of the 17 patients. The basis of lymph node classification was the presence of nodules in these patients could be divided into two groups (Figure 1).

The lymph nodes were classified as nodular lymphoma in 10 of the 17 patients. The nodules were composed of nodular poorly differentiated lymphoid cells with scant cytoplasm, inconspicuous nucleoli, and a high mitotic index (Figure 2). Survival was measured from the date of diagnosis. The median survival was 4.3 months (range 0.5 to 35 months).

Age	Diffuse Lymphomas		
	DLCL	DLCL	DLBL
6	4		9
42		36	36
29-65	12	65	2-65
6	1		4
6	0		4
1	4		5
4	11		31
11-12	7	17	8-120
25		16	85
50-100	13	32	14-95
2	4		7
41		10	13
13-110	4		3-45
12		0.5	4
13-110	0.2	1	2-35

DLCL = diffuse large cell; DLBL = diffuse poorly differentiated lymphocytic lymphoma.

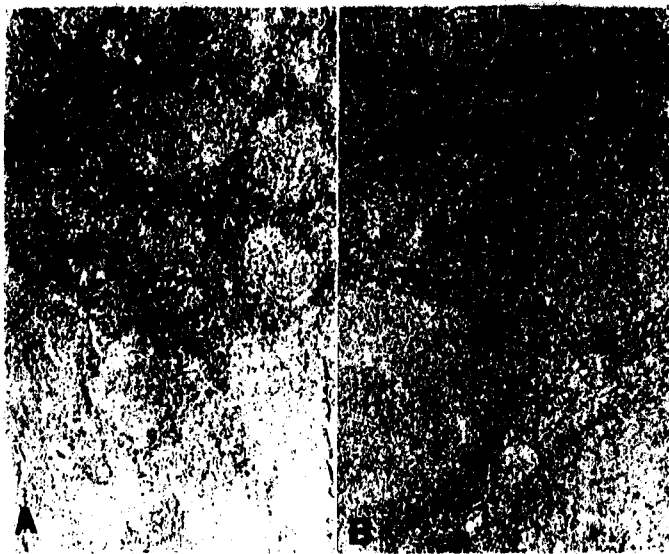


Figure 1. Nodular lymphomas. **A**, nodular lymphoma, poorly differentiated lymphocytic type (NPDL), group I. Well-defined nodules of uniform size and shape efface nodal architecture. **B**, nodular lymphoma, poorly differentiated lymphocytic type, blastic (NPDL-B1), group II. Nodules are variable in size and shape, occasionally with indistinct margins. Hematoxylin and eosin stain; magnification X 30, reduced by 13 percent.

as 75 percent reduction of all evident disease. Progression or stabilization of disease on therapy was considered no response. Survival was measured from the beginning of treatment.

RESULTS

Thirteen patients were leukemic at the time of presentation; in 17, a leukemic phase evolved later in the clinical course. The extent of peripheral involvement during the leukemic phase varied considerably, ranging from 13 percent malignant cells in a total white cell count of 7,000/mm³ to 95 percent malignant cells in a total white count of 208,000/mm³ (Table I). No patient had malignant cells in the peripheral blood in the absence of marrow involvement by tumor.

The histologic subclassification of the 30 patients with leukemic manifestations appears in Table I.

Nodular Lymphomas. In 11 of the 30 patients, the condition was classified as nodular lymphoma. On the basis of lymph node histologic and cytologic features, these patients could, in turn, be subdivided into two groups (Figure 1).

The lymph nodes from five patients, hereafter referred to as nodular group I, had the characteristics of nodular poorly differentiated lymphocytic lymphoma (NPDL) [15]. The neoplastic cells within the nodules consisted predominately of small cleaved irregular lymphoid cells with clumped compact nuclear chromatin, inconspicuous nucleoli and scant indistinct cytoplasm (Figure 2). Serial node biopsy specimens revealed retention of nodularity and little increase in mitotic index (Table II). No morphologic difference was observed among the nodes of the three patients who

were leukemic at the time of biopsy compared to the two in whom leukemic progression subsequently developed. Further, the histologic and immunologic features in these five patients (Table II) were indistinguishable from those in patients with NPDL in our population in whom leukemic involvement never developed.

Lymph nodes from the six patients who comprised nodular group II displayed cytologic features suggestive of less cellular differentiation. In five patients, who had no evidence of leukemic progression at the time of node biopsy, the majority of the cells within the nodules resembled lymphoblasts (Figure 2) [10], a finding not previously described in nodular lymphomas. In each of these cases, referred to as nodular poorly differentiated lymphocytic lymphoma, blastic (NPDL-B1), the predominant cells were of moderate size, 15 to 26 mu in diameter, with sparse pale-staining cytoplasm. The nuclear contours were round or oval with slight indentations. Convolved nuclei were not observed [25]. Nuclear chromatin was finely dispersed with 0 to 2 small basophilic, inconspicuous nucleoli. A subpopulation of small cleaved lymphocytes was also present. This histologic picture can be readily distinguished from the Rappaport nodular mixed lymphomas in which larger "histiocytic"-appearing cells, rather than the smaller blast cells, are associated with the small cleaved lymphocytes [15].

The mitotic index (Table II) in the primary biopsy specimens from these five patients was more than twice that observed in nodular group I, and a starry sky pattern was frequent within the nodules. Three of these patients underwent repeat node biopsies, all of which showed



Figure 2. Lymph node histology of non-Hodgkin's lymphoma. A, Nodular poorly differentiated lymphocytic, group I. Nuclei are cleaved and indented with coarsely clumped chromatin. B, nodular poorly differentiated lymphocytic, blastic, group II. Nuclei are round to oval with finely dispersed chromatin and inconspicuous nucleoli. Note similarity to cells in C. Occasional cells with indented nuclei (upper left) are noted. C, lymphoblastic lymphoma. Cytologic features resemble those of NPDL-B1 (B), although nuclear diameters are slightly smaller. Nuclear convolutions are not present in this example. D, diffuse "histiocytic" lymphoma. Cells are large with abundant indistinct cytoplasm, vesicular nuclei and prominent nucleoli. Hematoxylin and eosin stain; magnification $\times 1,000$, reduced by 13 percent.

progression to a diffuse growth pattern, an increased proportion of cells with blastic cytology, an increased mitotic index and prominent starry sky patterns.

The neoplastic cells seen in the peripheral blood during the leukemic phase (Figure 3) accurately reflected the contrast in lymph node histology between the patients in nodular group I and the five patients with blastic cytology in nodular group II.

The sixth patient in nodular group II had a primary diagnosis of nodular lymphoma, large cell ["histiocytic"] type (NLCL) [15]. Immunotyping revealed the two NPDL-B1 studied and the nodular large cell tumor to be of B cell origin. TdT activity was undetectable in these three patients.

The clinical features of these two subgroups of nodular lymphoma are compared in Table I. In the three patients in group I who presented with a leukemic blood picture, a complete remission was achieved after treatment with the combination of cytoxan, vincristine and prednisone (CVP), the duration ranging from seven to 24 months. Although all have had a relapse, two are still alive. None of the three relapses occurred in the peripheral blood, and a leukemic phase subsequently recurred in only one patient. Two patients in nodular group I became leukemic at 156 and 46 months after their initial presentation. Both are still living, one is in a continuing complete remission after treatment with CVP. In group I the median survival will exceed 54

TABLE II Clinical Features

	DLBL
Cases (no.)	
Degree of nodularity (mean)	
Mitotic index/hpf	
Primary biopsy (mean)	
Recurrences (mean)	
Immunotyping	
No. studied	
Results	
Terminal transferase (no. positive/no. studied)	

NOTE: Groups I + II = seen with blastic cytologic features = diffuse lymphoblastic
 * Based on three biopsies
 † Based on four biopsies

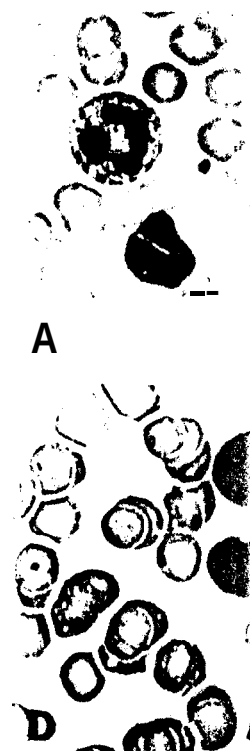


Figure 3. Peripheral blood of group I. Cells have sparse chromatin and small nucleoli. Occasional cells with finely distributed nuclear chromatin and deeply basophilic cytoplasmic nucleoli. Wright's stain; magnification $\times 1,000$, reduced by 13 percent.

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TABLE II Clinical Features

DLBL	Nodular Lymphomas			Diffuse Lymphomas		
	Group I—NPDL	Group II—NPDL-B1	Group II—NLCL	DWDL	DLCL	DLBL
Cases (no.)	5	5	1	6	4	9
Degree of nodularity (mean)	2.8	2.0	1.0	...	...	...
Mitotic index/hpf						
Primary biopsy (mean)	1.2	2.1	6.6	0.8	9.3	10.1
Recurrences (mean)	1.5*	12.5*	...	5.7*	...	...
Immunotyping						
No. studied	3	2	1	3	4	3
Results	All B	Both E	B	All B	2 B 1 null	2 T 2 null
Terminal transferase (no. positive/no. studied)	...	0/2	0/1	...	0/1	4/4

NOTE: Groups I + II = see text. NPDL = nodular poorly differentiated lymphocytic; NPDL-B1 = nodular poorly differentiated lymphocytic with blastic cytologic features; NLCL = nodular large cell; DWDL = diffuse well differentiated lymphocytic; DLCL = diffuse large cell; DLBL = diffuse lymphoblastic.

* Based on three biopsy specimens from two patients.

† Based on four biopsy specimens from four patients.

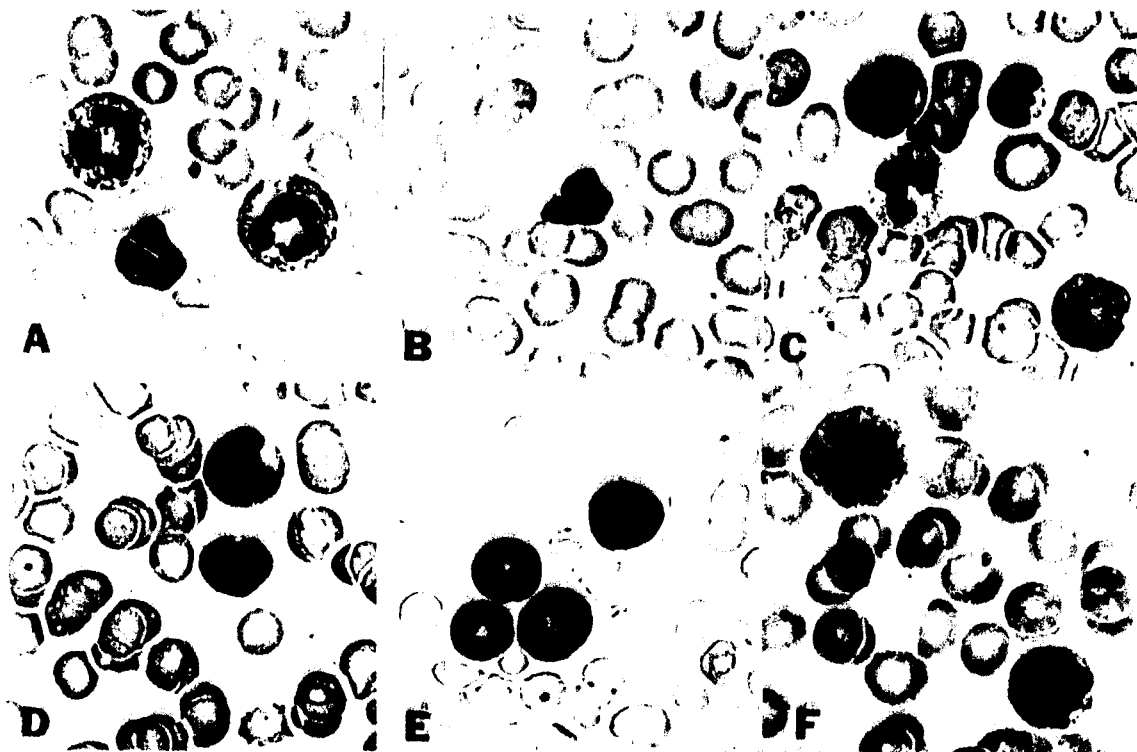


Figure 3. Peripheral blood involvement in non-Hodgkin's lymphomas. A and B, poorly differentiated lymphocytes of NPDL, group I. Cells have sparse cytoplasm; nuclei show deep grooves and condensed chromatin. C and D, Circulating atypical cells in NPDL, blastic. Predominant cells are blasts with a thin rim of basophilic cytoplasm. Nuclei have finely dispersed chromatin and small nucleoli. Occasional "buttock" cells or poorly differentiated lymphocytes of typical NPDL are seen. Same patient as in Figure 2B. (Wright's, X 1000). E, Lymphoblastic lymphoma. Leukemic lymphoblasts have extremely sparse cytoplasm, finely distributed nuclear chromatin and inconspicuous nucleoli. F, Diffuse "histiocytic" lymphoma. Circulating cells are large with deeply basophilic cytoplasm. Nuclei are markedly irregular in configuration with reticulated chromatin and prominent nucleoli. Wright's stain; magnification X 1,000, reduced by 13 percent.

months, and the median leukemic survival will exceed 43 months.

In the patients with blastic cytology in nodular group II (NPDL-B1), the duration of the preleukemic phase varied from 11 to 114 months; however, in contrast to those in nodular group I, the median leukemic survival was two months. During the leukemic phase in none of these patients was even a partial remission achieved. The patient in nodular group II with the large cell (histiocytic) histology entered a transient complete remission but had a relapse in sites of prior involvement including the peripheral blood.

Diffuse Well Differentiated Lymphocytic Lymphoma (DWDL). Six patients with leukemic manifestations were classified as having DWDL (Table II) [15]. Growth centers composed of large cells with vesicular nuclei and prominent central nucleoli were observed in two of them [26,27].

Although the histology and initial lymphocytosis in five patients (Table I) is compatible with an alternative diagnosis of chronic lymphocytic leukemia, the young ages and dominant nonhematologic disease manifestations—bulky adenopathy in all, gastrointestinal involvement in two, breast and cutaneous involvement in one each—prompted their inclusion in this series. The sixth patient became leukemic 10 months after diagnosis.

Treatment, which varied in intensity from oral alkylating agents to total body radiation plus CVP, produced no complete remissions. In three patients the condition subsequently converted to a less differentiated lymph node histology. In one it progressed to a diffuse lymphoma, poorly differentiated lymphocytic type with lymphoblastic features whereas in the other two diffuse large cell tumors developed of the undifferentiated pleomorphic type, compatible with Richter's syndrome.

Diffuse Large Cell Lymphoma (DLCL). Four patients in whom a leukemic phase evolved were identified as having a diffuse large cell lymphoma based on initial lymph node histology (Table II). In three it was subclassified as "histiocytic" (Figure 2) [15]. In one patient it was subclassified as undifferentiated, pleomorphic (non-Burkitt's) [15]. This was distinguished from the "histiocytic" type by a smaller cell size, less abundant cytoplasm and smaller although still distinct nucleoli.

In no patient was a complete remission achieved during initial treatment with combination chemotherapy, and a leukemic phase emerged a median of nine months after diagnosis (Table I) [Figure 3]. The number of malignant cells in the peripheral blood in these patients was the smallest among our subgroups, and the median survival after the occurrence of leukemia was only two weeks, the shortest in this series. The leukemic phase was associated with progressive disease in other sites.

Diffuse Lymphoblastic Lymphoma (DLBL). Nine patients with peripheral blood involvement were classified by initial lymph node histology as having diffuse lymphoblastic lymphoma (Table II). The predominant cell in these tumors had the cytologic features of a lymphoblast (Figure 2) [10]. Nuclear diameter was 12 to 20 μ m. Convolved nuclei were conspicuous in two patients, and evidence of lymphoid differentiation with progressive condensation of nuclear chromatin was observed in three [10,25]. Immunotypically, the four patients studied had null or T cell markers, and T cell activity was detected in each of them.

This histology was confined neither to the young nor to those with mediastinal involvement (Table I) [10,16,25]. Five of the nine patients were over age 30. In these older patients, extranodal sites of involvement—skin, gastrointestinal tract, bone, kidney, heart—were particularly common, and a mediastinal mass was encountered only once. Four patients were leukemic at diagnosis; in the remaining five, all of whom had no marrow involvement initially, a leukemic phase developed a median of 14 months after diagnosis (Figure 3). In either event, the leukemic phase of the disease was poorly responsive to treatment, with L-asparaginase proving to be the most active agent. The median survival in leukemic patients was four months whether peripheral blood involvement was an initial or late manifestation of disease.

Leptomeningeal Involvement. Meningeal lymphoma, documented by cerebrospinal fluid cytology on pathologic examination, developed in 15 of the 30 patients. In only two patients did meningeal involvement precede the onset of the initial leukemic phase, by two and 17 months, respectively. In five patients, meningeal involvement occurred during systemic remission.

COMMENTS

In this series, leukemic manifestations were observed in 14 percent of the 214 patients with non-Hodgkin's lymphoma. Although this figure is consistent with prior reports [3,5,28-30], it is more meaningful to consider incidence in relation to pathologic subtype. Peripheral blood involvement occurred in 10 percent of the patients classified as having NPDL (nodular group I) and in 6 percent of those classified as having DLCL. In our over-all population. In both of these histologic groups, which are the most common subtypes of non-Hodgkin's lymphoma, an analysis of lymph node histology, age, sex, stage, initial sites of involvement, including the marrow, and initial complete blood count did not distinguish nonleukemic patients in whom a leukemic phase was to evolve from those who have never evidenced peripheral blood involvement. Further, the patients with NPDL who were leukemic at the time of diagnosis could not otherwise be differentiated by the aforementioned parameters from their nonleukemic counterparts.

Seven patients with nodular lymphoma and blastic cytology (NPDL-B1) were noted among the 214 patients with non-Hodgkin's lymphoma. Although none was leukemic at the time of diagnosis five, discussed in this manuscript, had leukemic progression. Further, all nine

patients with DLCL, the over-all group, peripheral blood parameters, cytology, leukemic conversion, node cytology, pattern does suggest progression if it is a leukemic conversion. NPDL-B1, the leukemic phase.

However, there is a difference between DLCL and although convolved NPDL-B1 they are different. NPDL-B1 differ somewhat larger versus 10 to 15 μ m. plasma distinguish immunologically. Three patients with minimal leukemic, including monoclonal, consistent with it as a B cell tumor. four patients with the markers present was null, two were receptor without other patients with DLCL. contrast to the DLCL. Thus, this evidence is immunologically distinct.

In a previous study, et al. [31] described the leukemic phase who are patients with DLCL. correlative lymph node histology described either peripheral blood involvement or our patients with were present in the preleukemic phase.

Morphologic and a risk determinant which developed complication was lymphoblastic or fuse, and occurred series. This figure of survival of nonleukemic patients with non is comparable to

1. Flashman DH. case beginning coma and loss of consciousness. 177: 651.
2. Gall EA, Malt RA.

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patients with diffuse lymphoblastic (DLBL) tumors in the over-all group of 214 ultimately manifested peripheral blood involvement. Thus, in contrast to the parameters cited herein that were not predictive of leukemic conversion, lymphoblastic or blastic lymph node cytology in either a diffuse or a nodular growth pattern does seem to be a harbinger of leukemic progression if it is not already in evidence. Further, once leukemic conversion occurred in patients with NPDL-B1, the course resembled that of DLBL in its leukemic phase.

However, there appear to be certain differences between DLBL and our cases of NPDL-B1. Cytologically, although convoluted cells are common in DLBL, in NPDL-B1 they were not seen. Furthermore, the cells of NPDL-B1 differed from those of DLBL in having a somewhat larger cell size (15 to 25 μ in NPDL-B1 versus 10 to 15 μ in DLBL) and more abundant cytoplasm distinguishable in smears as a thin basophilic rim. Immunologically, these cases are also distinguishable. Three patients with NPDL-B1 were studied in the terminal leukemic phase, and all had B cell markers including monoclonal surface immunoglobulin. This is consistent with the recognition of nodular lymphoma as a B cell tumor. In contrast, the surface markers of the four patients with DLBL studied were in keeping with the markers previously reported for this disease: one was null, two were T, and one had an isolated C3 receptor without other B or T cell markers. Further, in two patients with NPDL-B1 studied TdT was absent in contrast to the ubiquitous presence of TdT in DLBL [19]. Thus, this evidence indicates that these tumors are biologically distinct.

In a previous review of follicular lymphoma, Spiro et al. [31] described five patients with a terminal leukemic phase who clinically and cytologically resemble our patients with NPDL-B1. However, in that study no correlative lymph node histologic features were described either prior to or during the leukemic phase. In our patients with NPDL-B1, cells with blastic cytology were present in lymph nodes during the often prolonged preleukemic phase.

Morphologic classification also proved important as a risk determinant of cerebrospinal fluid involvement which developed in 15 of the 30 leukemic patients. This complication was restricted to patients with either lymphoblastic or large cell histologies, nodular or diffuse, and occurred in 68 percent of these patients in this series. This figure is in contrast to the 11 percent incidence of nervous system involvement in unselected patients with non-Hodgkin's lymphoma [32,33], but it is comparable to the 65 percent incidence figure for

patients with DLCL and marrow involvement previously reported from this institution [34]. An evaluation of prophylactic central nervous system therapy seems warranted in these high risk histologies in which CNS disease both contributes to systemic failure and is difficult to eradicate once established.

Three clinical patterns of peripheral blood involvement in non-Hodgkin's lymphoma emerge from this study. In NPDL (group I), the relatively indolent natural history is reflected in the leukemic phase which appears to have little independent effect on the outcome of the illness. Indeed, the rate and degree of response, and the total survival of patients with NPDL who either present with peripheral blood involvement or in whom it develops approach these results in nonleukemic patients with NPDL. Bloomfield et al [35] have similarly reported that neither bone marrow nor peripheral blood involvement at diagnosis correlate with survival in NPDL. The total survival in patients with DWDL, and leukemic manifestations was also long, although the responsiveness to therapy and the survival of these patients was somewhat less than that in our nonleukemic patients with this histology [13] and less than that observed by Rappaport et al in his cases of DWDL and chronic lymphocytic leukemia.

At the opposite end of the spectrum, in diffuse large cell lymphomas, leukemic conversion appears as a terminal event associated with unresponsive disease in multiple sites and again exerts no important independent effect on prognosis. Between these poles are nodular lymphomas with blastic cytology (NPDL-B1) and diffuse lymphoblastic lymphoma. When it emerges in these patients, a leukemic phase becomes the dominant disease manifestation and signals an abrupt change in the clinical course with poor response to conventional treatment and rapid death. The almost invariable progression to an aggressive leukemic picture allows us to predict, and therefore possibly to avoid, a poor outcome in patients with this cytology and ostensibly more localized disease. Recently, extended disease-free survival has been achieved in pediatric patients with DLBL following intensive treatment with multiple chemotherapeutic agents in the preleukemic phase of the disease [36,37]. Preliminary studies indicate that this approach may be useful in adults with diffuse lymphoblastic tumors [38]. It is uncertain whether this success can be translated to patients with nodular lymphoma and blastic cytology as this disease is biologically different from DLBL despite its clinically similar leukemic course. However, increased recognition of this cytologic type of lymphoma is a necessary first step to devising more effective forms of therapy.

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