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## Histologic Progression in Non-Hodgkin's Lymphoma

By Susan M. Hubbard, Bruce A. Chabner, Vincent T. DeVita, Jr., Richard Simon, Costan W. Berard, Roy B. Jones, A. Julian Garvin, George P. Canellos, C. Kent Osborne, and Robert C. Young

We retrospectively evaluated the clinical course and biopsy specimens from 515 consecutive non-Hodgkin's lymphoma patients in an attempt to determine the clinical importance of documented changes in histology over time. Two-hundred and five of these patients had an initial diagnosis of nodular lymphoma and were reviewed for this analysis. Sixty-three underwent a repeat biopsy greater than 6 mo after initial diagnosis. In 23 patients, these repeat biopsies revealed a change in histology to a diffuse pattern and/or a change to a larger "histiocytic" cell type, while repeat biopsies for the other 40 (63%) disclosed persistence of a nodular pattern and no clear change in basic cell type. Progression from nodular lymphoma to diffuse histiocytic, mixed, or undifferentiated types of lymphomas of Rappaport was found in repeat biopsies obtained from 19 patients (30%). Prognosis for survival following a biopsy that demonstrated histologic change

was related to the histology demonstrated at the most recent biopsy and to the response to subsequent drug treatment. Survival following repeat biopsy for these 19 patients was significantly shorter than for the 40 patients whose histology remained nodular ( $p < 0.001$ ). However, attainment of a complete remission with intensive combination chemotherapy was associated with prolonged survival in eight patients and prolonged disease-free survival in one patient. Since prior treatment may compromise the ability to achieve a complete response to chemotherapy in patients with nodular lymphoma who develop an aggressive diffuse histology, the likelihood of histologic progression must be considered in the design of future clinical trials in nodular lymphoma. Histologic progression, while associated with a worsened prognosis, does not preclude attainment of a complete response to intensive chemotherapy.

**T**HE NON-HODGKIN'S LYMPHOMAS represent a heterogeneous group of diseases with differing natural histories and differing responses to treatment. These lymphomas are now recognized as encompassing two major types of disease that can be differentiated on the basis of histology and clinical course. In 1956, Rappaport proposed a pathologic classification system based on morphological appearance that has proved useful to clinicians because of its prognostic value.<sup>1</sup> The presence or absence of a nodular (follicular) pattern of lymph node involvement and the cytologic features of the malignant cells constitute the major diagnostic criteria. Lukes and Collins have proposed a different classification that stresses the appearance of individual cells as an indication of their origin.<sup>2</sup> Patients having a non-Hodgkin's lymphoma

with a nodular histologic pattern and a small cleaved cell type of Lukes and Collins (nodular poorly differentiated lymphoma) experience prolonged survival with radiotherapy, single agent chemotherapy, or combination chemotherapy, although most patients will develop recurrence of nodular lymphoma following successful therapy or demonstrate only partial responses to treatment.<sup>3-7</sup> In contrast, most patients with lymphomas that are diffuse in pattern and composed of large undifferentiated, so-called "histiocytic" cells have an aggressive clinical course with a median survival in the range of 3-6 mo when treated with radiotherapy or single agent chemotherapy.<sup>8</sup> However, patients with diffuse large cell lymphomas are highly responsive to combination chemotherapy. At least 40% of such patients achieve prolonged disease-free survivals with aggressive drug treatment.<sup>9-12</sup> Paradoxically, patients with indolent, "good prognosis" lymphomas are not curable with chemotherapy, while patients with diffuse, "poor prognosis" lymphomas may be cured with aggressive chemotherapy.

In 1956 Rappaport proposed, based on autopsy data, that nodular lymphomas tend to progress to diffuse forms of the same cellular composition.<sup>13</sup> We have previously reported that nodular lymphomas may evolve, albeit at varying rates of speed, from a nodular histologic pattern and small cleaved cell type to a diffuse mixed or large cell histologic type.<sup>14,15</sup> In this article, we present evidence that histologic progression is not uncommon in patients with nodular lymphomas and that this change is accompanied by a marked worsening of prognosis.

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*From the Scientific Information Branch, DCT, NCI, Bethesda, Md.; Clinical Oncology Program, DCT, NCI; Biometrics Branch, COP, DCT, NCI; Department of Pathology, St. Jude's Childrens Hospital, Memphis, Tenn.; Mt. Sinai Hospital, New York, N.Y.; Department of Pathology, Medical University of South Carolina, Charleston, S.C.; Sidney Farber Cancer Institute, Boston, Mass.; University of Texas, San Antonio, Tx.; Medicine Branch, NCI.*

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*Address reprint requests to Susan M. Hubbard, B.S., R.N., Scientific Information Branch, DCT, National Cancer Institute, Bethesda, Md. 20205.*

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## MATERIALS AND METHODS

### Patients

Five-hundred and fifteen patients diagnosed with non-Hodgkin's lymphomas whose initial diagnostic slides were classifiable and available for review were retrospectively evaluated for changes in histology during their clinical course. The initial hospital or outpatient visit to the Clinical Center, National Institutes of Health, occurred between 1953 and May 15, 1975, in all patients. Nodular histologies comprised 39.8% of all cases, while diffuse histologies comprised 60.2%. The most common histologic subtypes were nodular poorly differentiated lymphoma (20.2%) and diffuse histiocytic lymphoma (18.6%).

Two-hundred and five patients had an initial diagnosis of a nodular malignant lymphoma. In order to examine the incidence and clinical importance of histologic change in patients with nodular lymphoma at diagnosis, we retrospectively reviewed the clinical history and initial and subsequent biopsy specimens of all these patients. Date of diagnosis was taken as the date of the first biopsy classified as lymphoma by pathologic review at the NCI. All available biopsies taken before August 1975 were reviewed and classified. Histologic progression occurring less than 6 mo from diagnosis was not considered distinguishable from coexistence of nodular and diffuse lymphoma at the time of diagnosis. Patients with multiple histologic types of lymphoma coexisting at diagnosis have been described in a separate publication.<sup>16</sup> Sixty-three patients with nodular lymphoma had no conflicting histology in the first 6 mo and a classifiable biopsy taken greater than 6 mo after initial diagnosis.

### Histology

All antemortem biopsies were reviewed and classified by two pathologists (C.W.B., A.J.G.) according to a modified Rappaport scheme, discussed in a recent review.<sup>17</sup> A biopsy having any degree of nodularity was classified as nodular. The histologic pattern of lymphoma was considered to have undergone progression if a second biopsy, taken more than 6 mo after diagnosis, revealed a change from nodular poorly differentiated lymphocytic lymphoma (NPDL), nodular mixed lymphoma (NML), or nodular histiocytic lymphoma (NHL) to a diffuse lymphoma with a mixed cell, large cell, or undifferentiated cell type (DML, DHL, or DUL). Biopsies of bone marrow and liver were considered unclassifiable and invaluable for changes in histology.

### Clinical Evaluation

Pretreatment evaluation included complete blood counts and routine liver function tests, chest roentgenogram, intravenous pyelography, lymphangiography (after 1968), and percutaneous biopsies of liver and bone marrow. Since 1971, more extensive staging has been routinely employed.<sup>18</sup> When a complete remission was attained by clinical evaluation, procedures that were initially positive were repeated to verify complete remission status. In addition, since 1965, accessible recurrent tumors were rebiopsied when appropriate to document relapse from complete remission and to assess histology at the time of disease progression.

### Therapy

The patients in this study were treated as part of a series of protocol studies carried out by the Medicine Branch, Pediatric Oncology Branch, and Radiation Oncology Branch of the NCI over the 22 yr encompassed by this review. Chemotherapy included the use of several multiagent regimens (CVP, MOPP, C-MOPP,

BACOP) described elsewhere.<sup>9,10,19,20,22,23</sup> Radiation therapy (total nodal, total body, or involved field) was used alone or in combination with chemotherapeutic agents in patients with nodular histologies. These regimens have also been described.<sup>3,21</sup>

### Data Analysis

Total survival time was calculated from the date of the initial diagnostic biopsy to the date of death. Survival following histologic progression was calculated from the date of the first biopsy that documented histologic progression. For patients who remained nodular at repeat biopsy, survival after repeat biopsy was calculated from the date of the first biopsy that was performed more than 6 mo following diagnosis. For patients with histologic progression, histologic conversion was observed in the first biopsy that was performed greater than 6 mo after initial diagnosis in all but three patients. These 3 patients demonstrated histologic progression on the second biopsy taken more than 6 mo after diagnosis. In three patients with histologic progression, the diffuse lesion was identified simultaneously with a biopsy that showed persistent nodular lymphoma in a different site. All repeat biopsies that were classified as diffuse were considered as a group for analysis and all those that remained nodular were considered as another group.

Two statistical methods were used for comparing survival distributions. The first was the straight forward Mantel-Haentzel test of survival from rebiopsy.<sup>22</sup> Survival from diagnosis was compared using the generalized Mantel-Haentzel test for evaluation of response-time data involving transient states.<sup>23</sup> The latter method was used to adjust for variability in rebiopsy times.

## RESULTS

Table 1 shows the initial histologic diagnosis and subsequent biopsy results in the 63 patients with nodular lymphoma who had a repeat biopsy greater than 6 mo after initial diagnosis. In 40 patients repeat biopsy revealed persistence of a nodular pattern and no clear change in cell type. In 17 patients, repeat biopsy revealed a change in histology from a NPDL (8 patients) or NML (9 patients) to DML, DHL, or DUL. Two additional patients, with nodular histiocytic lymphoma, had repeat lymph node biopsies that revealed histologic progression to DHL (1 patient) and DUL (1 patient). In an additional 4 patients, the repeat biopsy revealed a diagnosis of diffuse well differentiated (1 patient) or diffuse poorly differentiated (3 patients) lymphoma. These 4 patients were not considered further in this analysis.

Table 2 shows the sites of repeat biopsy in the 19

**Table 1. Initial and Subsequent Diagnoses of 63 Patients With Nodular Lymphoma Rebiopsied Greater Than 6 mo After Initial Diagnosis**

Initial Diagnosis	Subsequent Diagnosis		
	NPDL or NM	DM, DH, or DU	DWDL or DPDL
NPDL	38	27	8
NM	23	13	9
NH	2	0	2
Total	63	40	19

**Table 2. Classified Sites of Repeat Biopsy**

	Nodular → Nodular	Nodular → DM, DH, or DU
Nodes only	35 (87.5%)	10 (52.6%)
Nodes and other	4*	5‡
Other only	1†	4§

\*Three cases spleen and one case pleura.

†Breast.

‡Two cases spleen, one case stomach, one case ileum, one case inner canthus of eye.

§Two cases stomach, one case spleen, one case skin and stomach.

patients who had histologic progression from nodular lymphoma to DML, DHL, or DUL. In 13 of these 19 patients, progression to a diffuse lymphoma of mixed or large cell type was detected by biopsy of a lymph node, while in 6 patients, the initial diagnosis of histologic progression was made on the basis of a biopsy obtained from an extranodal site [stomach (3 patients), terminal ileum (1 patient), spleen (1 patient), and the inner canthus of the eye (1 patient)]. In the latter patient, a subsequent lymph node biopsy confirmed the diagnosis of diffuse mixed lymphoma first made on extranodal material. Thus, in 14 of 19 patients (74%), histologic progression from a nodular lymphoma to diffuse mixed or large cell lymphoma was demonstrated on a repeat lymph node biopsy, with or without extranodal sites of involvement. In the five other cases, the diagnosis of histologic progression from NPDL to DHL was exclusively based on the histology of new extranodal sites of tumor involvement.

The clinical features of the 19 patients who had histologic progression were compared with those of the 40 patients who exhibited unchanged histology during the period of this study. The groups were similar with regard to the type of primary therapy used and the response to therapy (Table 3). Patients who subsequently demonstrated progression of tumor histology tended to have an earlier stage at the time of initial presentation, and a greater percentage (21% versus 10%) had received local radiation therapy as their primary treatment.

The impact of histologic progression on further treatment response and survival was determined by comparing the clinical course of patients who demonstrated progression at repeat biopsy with the course of those who retained a nodular histology. As shown in Fig. 1, the survival from time of rebiopsy was markedly longer for patients who continued to have a nodular histology on repeat biopsies. The estimated median survival for the patients who remained nodular following their first repeat biopsy is 77 mo (95% confidence limit  $\geq 64$  mo), while patients whose repeat

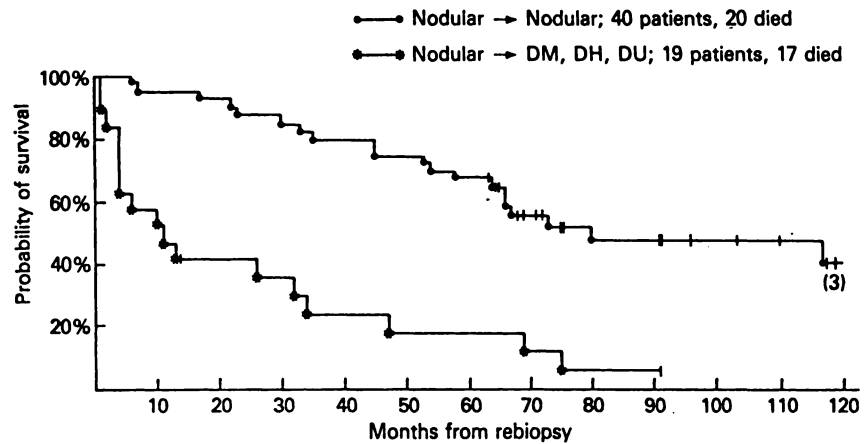
biopsies demonstrated histologic progression lived a median of only 11 mo from the time of rebiopsy (95% confidence limit 4–34 mo).

In order to eliminate the possibility that the difference in survival after biopsy could be accounted for by the repeat biopsy being taken later in the clinical course of the patients showing progression, we examined the interval from diagnosis to repeat biopsy. The median time to repeat biopsy was 25 mo for the 19 patients whose histologic type changed from nodular lymphoma to DML, DHL, or DUL. The 40 patients with nodular lymphoma who did not experience a change in histology had a median interval of 27 mo from the time of initial diagnosis to the first rebiopsy. The distributions were also very similar (Fig. 2). Thus, the shorter postbiopsy survival of patients demonstrating histologic progression cannot be explained by a longer interval from diagnosis to repeat biopsy. As might be expected, the overall survival from initial diagnosis was significantly shorter for patients demonstrating histologic progression as compared to those who retained a nodular histology (48 mo versus 92 mo,  $p < 0.001$ ).

The comparison of treatments for patients after repeat biopsy are summarized in Table 4. Twelve

**Table 3. Patient Characteristics**

	Nodular → Nodular	Nodular → DM, DH, or DU
CS: I	2 (5%)	5 (26.3%)
II	3 (7.5%)	3 (15.8%)
III	31 (77.5%)	10 (52.6%)
IV	4 (10%)	1 (5.3%)
PS: I	2 (5%)	4 (22.2%)
II	1 (2.5%)	2 (11.1%)
III	15 (37.5%)	4 (22.2%)
IV	22 (55%)	8 (44.4%)
Unknown		1
Age (median)	44.5	47
Sex (M:F)	21:19	10:9
Year of diagnosis		
Before 1/69	15 (37.5%)	4 (21.1%)
After 1/69	25	15
Primary therapy		
Single agents	1 (2.5%)	1 (5.3%)
Combination chemotherapy (CC)	16 (40%)	6 (31.6%)
Involved field radiotherapy	2 (5%)	4 (21.1%)
Extended field radiotherapy	2 (5%)	0
Total nodal irradiation (TNI)	3 (7.5%)	3 (15.8%)
Total body irradiation (TBI)	10 (25%)	3 (15.8%)
TNI + TBI	1 (2.5%)	0
CC + TBI	0	1 (5.3%)
Untreated	5	1
Primary response		
Complete response (CR)	24 (68.6%)	10 (55.6%)
Partial remission (PR)	9	7
Disease progression (DP)	2	1



**Fig. 1.** Survival from time of rebiopsy for patients whose histology remained nodular compared to those who developed diffuse mixed (DM), diffuse histiocytic (DH), or diffuse undifferentiated (DU) lymphoma.

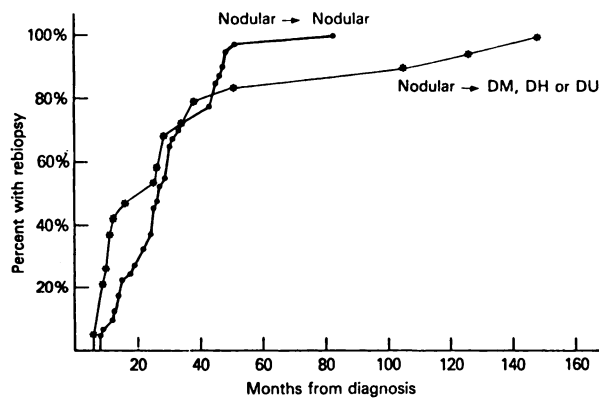
patients with histologic progression were initially treated with intensive combination chemotherapy regimens and 6 (50%) achieved a complete remission. Two of 4 patients who failed to achieve a complete response to radiotherapy, were subsequently treated with combination chemotherapy and achieved complete remissions. One patient, who was initially diagnosed with NPDL and relapsed with DHL, remains in continuous complete remission 83 mo after the end of all treatment. Median duration of complete remission for these 8 patients was 11 mo and median survival following repeat biopsy was 40.5 mo (range 12–88+ mo). Median survival after repeat biopsy in the 11 patients who did not achieve complete remission was 4 mo (range 1–26 mo). Four of the 8 patients who achieved complete remissions have expired and 3 were free of lymphoma at autopsy. Causes of death in these 3 patients were pancytopenia and sepsis (2 patients) and acute leukemia (1 patient).

In addition to the 63 patients described here, there were 116 patients with nodular lymphoma who had no

conflicting diagnoses within the first 6 mo and for whom there were no subsequent classifiable biopsies during the course of this study. Because of this, it is difficult to estimate what the true frequency of histologic progression is in the entire population. A prospective study, with uniform criteria for repeat biopsy, will be required to establish the true frequency.

**DISCUSSION**

Other investigators have now reported the occurrence of histologic transformation from nodular to diffuse lymphoma during the clinical course of selected patients and have suggested that this change occurs as the result of a transformation of the original cell line.<sup>24-25</sup> Woda and coworkers have reported an interesting transformation from a nodular poorly differentiated lymphoma to a diffuse histiocytic lymphoma in a single patient.<sup>25</sup> This patient had a



**Fig. 2.** Time to rebiopsy distributions. For patients who remained nodular (o--o), the date of first repeat biopsy was used to calculate this interval. For those who demonstrated progression to DML, DHL, or DUL (•---•), the date of the first repeat biopsy that revealed a diffuse histology was used.

**Table 4. Primary Therapy After Repeat Biopsy**

Therapy	Nodular → Nodular	Nodular → DM, DH, or DU
Single agents (SA)	4 (10%)	1
Combination chemotherapy (CC)†	20 (50%)	12 (63.2%)
Involved field radiotherapy (IF)	1	1
Extended field radiotherapy	0	0
Total nodal irradiation (TNI)	1	0
Total body irradiation (TBI)	9 (22.5%)	1
TBI + CC	2	0
TBI + IF	0	2
Other combinations*	2	0
None or unknown	1	2
<b>Total</b>	<b>40</b>	<b>19</b>
<b>Response</b>		
Complete remission (CR)	24 (61.5%)	6 (35.3%)
Partial remission (PR)	11	3
Disease progression (DP)	4	8

\*IF + SA (1 patient); TBI + TNI (1 patient).

†Two patients received CC + IF.



monoclonal protein (IgG lambda) associated with the malignant cells of the initial diagnostic biopsy. The majority of cells in a second biopsy, obtained when the patient relapsed with diffuse histiocytic lymphoma, retained the same type of cytoplasmic IgG lambda immunoglobulin. Since nodular lymphomas are thought to arise from B cells that contain monoclonal immunoglobulin, persistence of a monoclonal B-cell marker after histologic progression to a diffuse lymphoma suggests transformation of the original malignant clone of lymphocytes.<sup>25-27</sup>

Erickson and coworkers have observed cytologic transformation in 13 of 125 patients with nodular small cleaved cell lymphoma to diffuse lymphomas of large and small cell type.<sup>28</sup> In two cases that were studied prior to and following cytologic transformation, surface immunoglobulin heavy and light chain types remained constant. These data are consistent with the hypothesis that the development of diffuse large cell lymphomas in patients who previously had nodular poorly differentiated lymphoma represents a histologic transformation of the original B-cell line rather than the development of a second malignant clone. However, the true rate and frequency of this evolution are not known, nor is it established whether the change in histology is related to or accelerated by therapy.

This analysis of the clinical course and histologic findings on repeat biopsy of patients with nodular lymphoma has disclosed a substantial frequency of conversion of these malignancies to a diffuse mixed or diffuse large cell lymphoma. Of the 203 patients admitted to the NCI with a diagnosis of nodular lymphoma from 1953 to 1975 who had no conflicting histologies in the initial 6 mo, 63 subsequently underwent a repeat biopsy of a lymph node or extranodal mass, and 23 of the 63 patients had new histologic evidence of a diffuse lymphoma. In 19 patients, the histologic change was considered to represent a clear "progression" of histologic type, since the change was from a NPDL or NML lymphoma to DML or DHL in 17 patients and from NHL to DHL in biopsies taken from lymph nodes in the remaining 2 patients.

The true frequency of histologic progression in patients with nodular lymphoma cannot be reliably estimated from the current study because only 31% of patients underwent a rebiopsy during this period. Prospective long-term studies, with aggressive rebiopsy of new lesions, particularly those in extranodal sites, will be required to establish the actual frequency of histologic progression.

Previous clinicopathologic studies of patients with non-Hodgkin's lymphomas have conclusively demon-

strated that NPDL and NML lymphomas are associated with indolent clinical courses and long-term survival, while DML, DHL, and DUL are rapidly progressive lymphomas that are associated with median survivals of less than 1 yr unless a complete remission is achieved with intensive therapy.

The clinical course of patients whose biopsies demonstrated histologic progression reflected a clear change in the pace of their disease, as compared to the course of patients whose lymphoma remained nodular. The median survival of 11 mo after repeat biopsy was significantly shorter for the patients with histologic progression as compared to 77 mo for those whose tumor remained nodular. In 12 of the 19 patients with histologic progression, a diagnostic biopsy was performed to document disease in extranodal sites. However, in 14 of these 19 patients, the assessment of histologic progression was detected or confirmed by lymph node pathology. In 5 patients, the assessment was made on a clear change in cell morphology from a small cleaved cell type to a large cell type detected in extranodal sites.

These results suggest that histologic progression is associated with tumor dissemination to extranodal sites. However, since thorough restaging was not performed in most patients at the time of repeat biopsy, the degree of extranodal extension of lymphoma is unknown in patients whose biopsy histology remained nodular. Patients whose repeat biopsies showed histologic progression were more likely to be rebiopsied in extranodal (and particularly intraabdominal) sites, but prospective studies employing thorough restaging at the time of repeat biopsy will be required to verify an association between histologic progression and tumor dissemination.

The use of aggressive combination chemotherapy in 14 patients with histologic progression produced complete remissions in 8 patients. Median survival of complete responders after histologic conversion was approximately 40 mo as compared to 4 mo in those who did not achieve complete remissions. While only one patient has achieved prolonged disease-free survival, the value of intensive chemotherapy in this group of patients is suggested by our experience.

Six of the 14 patients treated with combination chemotherapy, including 3 who achieved complete remission, had previously been treated with alkylating agents during the nodular phase of their disease. Resistance to alkylating agent therapy may have occurred in some of these patients, compromising the ability to achieve complete remission following histologic conversion. Prior exposure to alkylating agents may have played a role in the development of acute

leukemia in the patient who achieved a complete remission.

We were unable to identify clinical features at the time of initial presentation that predisposed patients to histologic progression. None of the factors examined, including stage, type of therapy, age, or sex appeared to influence the frequency of this process. The change to a more aggressive histology may represent an inherent potential of nodular lymphomas, similar to the blastic transformation of chronic granulocytic leukemia.<sup>15,29</sup> In most biopsy specimens from patients with nodular lymphoma it is possible to identify, if only in minor proportion, large cells that are indistinguishable from the malignant "histiocyte" of DHL. Composite lymphomas, composed of areas of nodular and diffuse architecture in a single lymph node have been detected by Kim in 3 of 84 untreated patients with non-Hodgkin's lymphoma.<sup>30</sup> In addition, approximately 10% of patients with non-Hodgkin's lymphoma have multiple histologic types of lymphoma identified in the biopsies taken during the staging evaluation.<sup>16,31</sup> These findings, together with the results of the present study and previous case reports and retrospective studies, suggest that nodular lymphomas tend to evolve toward a more diffuse pattern of lymph node involvement and a larger, less differentiated, cell type. In some cases, it is possible that the "nodular phase" of disease is not recognized clinically, particularly in those cases that undergo rapid evolution to an aggressive phase of their disease.

Another factor contributing to histologic progression may be therapy. Ionizing radiation and chemotherapy, especially alkylating agents, are known to be mutagenic for bacterial and mammalian cells, and may hasten the appearance of a more aggressive cell type. The early use of chemotherapy or intensive radiotherapy in patients with nodular lymphomas may increase the risk of selection of drug-resistant clones and compromise subsequent therapy when the disease converts to an aggressive histologic pattern.<sup>32</sup> An alternative explanation for the apparent histologic progression is initial discordance in sites that have not been biopsied.

Our findings suggest that current concepts concerning the treatment of nodular lymphomas should be reevaluated, especially in histologic subtypes such as NPDL where combination chemotherapy has yet failed to achieve durable complete remissions. The optimum approach may well consist of observing patients with indolent nodular lymphoma until they evolve a diffuse histology and then to treat for cure with aggressive combination chemotherapy.

Portlock and Rosenberg have reported a retrospec-

tive series of 21 asymptomatic patients with indolent nodular poorly differentiated lymphoma in whom initial therapy was withheld until required for control of symptoms of disease progression. In this select group, the median time before treatment was initiated was 32 mo.<sup>33,34</sup> These data support the idea that a conservative "watch and wait" approach should be evaluated as an alternative to aggressive therapy as initial management in selected patients with nodular lymphoma. In order to prospectively evaluate both the pace of disease progression and the value of early treatment in unselected patients with nodular lymphoma, we are prospectively evaluating a "watch and wait" approach to aggressive combination chemotherapy at the National Cancer Institute.<sup>15</sup> Patients with nodular lymphoma are randomized to receive close follow-up and no initial treatment or an intensive combination chemotherapy regimen. Patients randomized to "watch and wait" will receive only limited, local radiotherapy until they develop disease that cannot be adequately controlled with 2500 rads or until histologic progression occurs. This trial will provide a true estimate of the frequency of histologic progression in minimally treated patients and allow comparison of a conservative approach to aggressive chemotherapy in unselected patients. It will also enable us to examine whether histologic progression occurs more rapidly or frequently after intensive treatment, and whether patients who exhibit histologic progression after treatment are less responsive than patients who develop histologic progression without treatment, or those who are diagnosed with DHL, DML, or DUL de novo.

#### SUMMARY

Histologic progression was seen in 19 of 63 (30%) patients with nodular lymphoma who were rebiopsied. Prolonged survival can still be expected in patients with non-Hodgkin's lymphomas if repeat biopsies exhibit a nodular histology. Patients whose repeat biopsies remained nodular survived a median of 77 mo from the time of repeat biopsy as compared to 11 mo for those whose biopsy was diffuse. However, survival following histologic progression was greatly influenced by response to chemotherapy. A complete response, associated with prolonged survival was achieved in 8 patients treated with combination chemotherapy. Histologic progression should be suspected in all patients with nodular lymphoma who respond poorly to therapy, undergo clinical progression during treatment, relapse, or develop disease in new extranodal sites. In these settings, a biopsy should be obtained whenever possible to assess changes in histology.

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