Nodular Histiocytic Lymphoma: An Aggressive Nodular Lymphoma With Potential for Prolonged Disease-Free Survival


Nodular histiocytic lymphoma (NH) is uncommon, and its natural history is not well defined. Of 473 patients with non-Hodgkin's lymphoma, we found 16 (3.4%) with NH. Most patients (13/16) presented with pathologic stage (PS) III or IV disease, including 7 with liver involvement. One patient (PS III) was initially treated with cyclophosphamide alone, and 4 patients received only radiotherapy, and none were long-term survivors. Eleven patients received combination chemotherapy, and 8 achieved complete remission. Only one of these patients relapsed and died at 19 mo; the other 7 continue in complete remission without maintenance therapy with a minimum followup of 4.5 yr. The survival of the entire group of patients with NH is intermediate between that of the other nodular lymphomas and diffuse histiocytic lymphoma.

Nine of 16 patients had either a repeat lymph node biopsy during the course of their disease or lymph node examination at autopsy. Lymph node histology in the majority converted to a diffuse, less differentiated subtype of lymphoma. NH has a natural history similar to that of diffuse histiocytic lymphoma and should be approached with the same therapeutic strategy.

The Rappaport Classification of the non-Hodgkin's lymphomas has proven useful to clinicians because it identifies subsets of patients that display characteristic clinical features, response to therapy, and prognosis. In general, diffuse lymphomas (except the well differentiated subtype) more frequently present in extranodal sites and tend to have a more aggressive natural history and more "unfavorable" prognosis than nodular lymphomas. Recent studies, however, have clearly demonstrated that long-term disease-free survival can be achieved with aggressive therapy of certain diffuse subtypes. In contrast, nodular lymphomas, although usually widespread at the time of diagnosis, display an indolent course and prolonged survival. Although nodular lymphomas are considered to have a "favorable prognosis," prolonged disease-free survival is uncommon.

The clinical features of the nodular lymphomas have primarily been derived from studies of poorly differentiated lymphocytic lymphoma (NPDL) and mixed lymphocytic-histiocytic (NML), the two most common subtypes. However, the clinical characteristics of nodular histiocytic lymphoma (NH) have not been well defined because of the relative infrequency of this pathologic subtype. We have recently reviewed a large number of patients with non-Hodgkin's lymphoma treated and followed at the National Cancer Institute. In the present study, we have examined the subset of patients with the diagnosis of NH in order to better define the clinical features of this disease.

Materials and Methods

Patients

There were 521 patients with a diagnosis of non-Hodgkin's lymphoma admitted to the National Institutes of Health between July 1, 1953 and May 15, 1975. Thirty-seven patients were excluded from analysis because they were not referred within 12 mo of diagnosis. Eleven additional patients were unevaluable because of insufficient biopsy material for histopathologic review or because of ambiguity in histopathologic diagnosis. Clinicopathologic correlations were determined for the remaining 473 patients.

Histopathology

All biopsies were reviewed and classified according to the Rappaport scheme by two pathologists (C.W.B. and A.J.G.). Disagreements were resolved by reconciliation. Lymphomas were classified as histiocytic if the predominant cell was the large cell type; they were considered nodular if any degree of nodularity was present. In addition, lymph node nodularity was semiquantitatively assessed according to the histologic prominence of nodules (1+ — minimal, 4+ — prominent) and the estimated proportion of the lymph node displaying a nodular pattern (25%, 50%, 75%, or 100%). Of the 473 patients, 16 were classified as NH.

Clinical Evaluation and Staging

Although some evolution of staging approaches occurred over the duration of this review, all patients with NH underwent extensive pretreatment clinical evaluation. In addition to complete blood counts and chemistries and chest radiographs, 15 of 16 patients had bipedal lymphangiograms, and all 16 had bone marrow aspiration and biopsy. Thirteen of 16 had percutaneous and/or laparoscopically directed liver biopsy, and 8 of 16 underwent staging laparotomy.

Treatment

All 16 patients with NH were previously untreated for lymphoma and most (15/16) were treated according to one of several ongoing studies of chemotherapy and/or radiation therapy at the National Cancer Institute. One patient, who had polycythemia rubra vera at the time of diagnosis, was treated off study with single-agent chemotherapy (cyclophosphamide). All other patients treated initially with chemotherapy were given various drug combinations.
These included: CVP, consisting of cyclophosphamide (400 mg/sq m/day for 5 days), vincristine (1.4 mg/sq m on day 1) and prednisone (100 mg/sq m/day for 5 days), administered in 21-day cycles, MOPP, consisting of 28-day cycles of mechlorethamine (6 mg/sq m on days 1 and 8), vincristine (1.4 mg/sq m on days 1 and 8), procarbazine (100 mg/sq m/day on days 1–14), and prednisone (40 mg/sq m on days 1–14); C-MOPP, which is identical to MOPP except that cyclophosphamide (650 mg/sq m on days 1 and 8) is substituted for mechlorethamine; and BACOP, consisting of cyclophosphamide (650 mg/sq m on days 1 and 8), vincristine (1.4 mg/sq m on days 1 and 8), adriamycin (25 mg/sq m on days 1 and 8), bleomycin (5 U/sq m on days 15 and 22), and prednisone (60 mg/sq m on days 15–28) administered every 28 days.

Data Analysis.

Clinical data were collected by reviewing the clinical records using a standarized form. The data were stored for later computer-assisted retrieval and analysis. Histopathologic interpretations were also computerized. Unless otherwise stated, survival time was determined from the date of diagnosis of lymphoma. Survival data were analyzed by the method of Kaplan and Meier and the curves compared by Gehan’s generalized Wilcoxon test (two-sided).10

RESULTS

Study Population

NH is an uncommon histologic subtype of lymphoma (Table 1). Only 16 (3.4%) of 473 consecutive patients with lymphoma referred to the NIH were considered to have this subtype after careful histopathologic review. As previously reported, nodular poorly differentiated lymphocytic (18.6%) and diffuse histiocytic (19.2%) were the two most common varieties.4,11 The median age of the 16 patients with NH was 51 yr (range 29–67), and 9 patients were male.

Results of Staging

The majority of patients demonstrated widespread disease at the time of diagnosis. Only 3 of the 16 patients (18.7%) presented with localized disease (PS I and II), although one of these patients officially classified as PS I had suggestive focal infiltrates of atypical lymphocytes in the bone marrow and liver. Thirteen of the 16 patients (81.2%) presented with PS III or IV disease). Of the 9 patients with PS IV disease, 3 had bone marrow involvement and 7 had liver involvement. None of the patients with NH presented as an extranodal primary tumor, and only 4 patients complained of “B” symptoms, such as weight loss, fever, or night sweats. Thus, similar to other nodular lymphomas, patients with NH usually have advanced stage disease at the time of diagnosis.

Response to Treatment

Patients with non-Hodgkin’s lymphomas were admitted to the NIH for study and treatment starting in 1953. However, the first patient with NH was not seen until 1965. Thus, most of these patients were treated by relatively contemporary radiotherapeutic techniques and/or combination chemotherapy (Table 2). Four patients received some form of radiation therapy alone as their initial treatment. These included one PS I who received total nodal radiation, one PS II treated to involved fields, and two PS IV

Table 1. Distribution of 473 Patients According to a Modified Rappaport Classification

<table>
<thead>
<tr>
<th>Histology</th>
<th>Number of Patients (%)</th>
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<tbody>
<tr>
<td></td>
<td>Nodular</td>
</tr>
<tr>
<td>Well differentiated lymphocytic</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Poorly differentiated lymphocytic</td>
<td>88 (18.6)</td>
</tr>
<tr>
<td>Mixed lymphocytic histiocytic</td>
<td>76 (16.1)</td>
</tr>
<tr>
<td>Histiocytic</td>
<td>16 (3.4)</td>
</tr>
<tr>
<td>Undifferentiated pleomorphic</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Burkitt’s</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>180 (38.1)</td>
</tr>
</tbody>
</table>

Table 2. Nodular Histiocytic Lymphomas: Response to Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PS (No.)</th>
<th>Response*</th>
<th>No. CR</th>
<th>No. Dead</th>
<th>Median Survival (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>All (4)</td>
<td>PD PR CR</td>
<td>1 1 2</td>
<td>2 2 4†</td>
<td>21 mo (21–32)</td>
</tr>
<tr>
<td></td>
<td>I (1)</td>
<td>— — 1</td>
<td>1 1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>II (1)</td>
<td>— 1 —</td>
<td>— 1 1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>IV (2)</td>
<td>1 — 1</td>
<td>1 1 2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Single drug</td>
<td>All (11)</td>
<td>1 8 2</td>
<td>1 5‡</td>
<td>Not reached at 60+ (8–135+)</td>
<td></td>
</tr>
<tr>
<td>Combination chemotherapy</td>
<td>I (1)§</td>
<td>— — 1</td>
<td>0 0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>III (3)</td>
<td>— 1 2</td>
<td>0 1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>IV (7)</td>
<td>1 1 5</td>
<td>1 4‡</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>(16)</td>
<td>3 3 10</td>
<td>3 10</td>
<td>31 mo</td>
<td>—</td>
</tr>
</tbody>
</table>

*PD, progressive disease; PR, partial remission; CR, complete remission.
†One patient died of drug toxicity after a chemotherapy induced complete remission following relapse.
‡One patient died of a cerebral hemorrhage while still in complete remission at 76 mo.
§One patient was classified as PS I; however, chemotherapy was given following radiotherapy because of the strong suspicion of more advanced stage disease (see text).
patients treated with total nodal plus whole abdomen and total body radiation, respectively. Eleven patients received combination chemotherapy as initial treatment. One PS I patient received C-MOPP chemotherapy in addition to extended field radiotherapy because of several factors suggestive of more advanced stage disease: (A) the presence of weight loss, fever, and night sweats, and (B) the presence of focal areas in the bone marrow and liver of atypical lymphocytes suspicious for but not diagnostic of lymphoma. The remaining 10 patients, all of whom had advanced PS III (3) or IV (7) disease, were treated with combination chemotherapy alone, including MOPP (2), CVP (1), C-MOPP (6), and BACOP (1).

Patients with NH initially responded well to either radiation therapy or chemotherapy (Table 2). Ten of 16 patients (62.5%) achieved a pathologically documented complete remission, 3 evidenced a partial remission, and 3 had progressive disease. When subdivided by treatment, 2 of 4 patients given radiation therapy and 8 of 11 patients given combination chemotherapy achieved complete remission. The patient with polycythemia rubra vera treated with only cyclophosphamide had progressive disease and died of lymphoma 29 mo after initiation of treatment.

Although the complete remission rates were comparable in patients treated initially with radiotherapy or combination chemotherapy, the duration of remission and survival was better in patients given chemotherapy, despite the fact that 10 of 11 patients had advanced stages of disease (Table 2). The two patients achieving complete remission (including one with laparotomy-proven PS I disease) with radiotherapy relapsed rapidly (6 and 14 mo). One of these patients (PS I, total nodal radiotherapy) relapsed in paraaortic, mesenteric, and pelvic lymph nodes as well as the liver. The other patient (PS IV liver, total nodal plus whole abdomen) relapsed in paraaortic lymph nodes. All 4 patients given radiotherapy have died, although one of these patients died of drug toxicity after a chemotherapy induced complete remission following relapse from radiation therapy. The median survival of these 4 patients was short (21 mo). In contrast, only 1 of 8 patients achieving complete remission with combination chemotherapy has relapsed; 7 are long-term disease-free survivors with a minimum follow-up of 4.5 yr. It should be emphasized that no maintenance therapy was given to any patients in this study. Six of the 7 patients achieving long-term remission received only 6 cycles of chemotherapy at 3-wk (CVP) or 4-wk (C-MOPP) intervals. The other patient required 10 cycles of C-MOPP in order to eliminate residual liver involvement determined by serial liver biopsy at laparoscopy. Of the 11 patients treated with combination chemotherapy, only 5 have died, including one complete responder who died of a cerebral hemorrhage while still in remission more than 6 yr after diagnosis. The median survival of the combination chemotherapy group has not been reached at 60+ mo (8–135+).

**Correlation With Histopathology**

In the majority of our patients diagnosed as NH, only 50% or less of the tissue examined demonstrated a nodular (follicular) architecture (Table 3). In 10 of 16 patients, a significant proportion of the biopsy showed a diffuse pattern; only 6 patients demonstrated a follicular pattern over the entire specimen. Furthermore, when the degree of nodularity was graded semi-quantitatively, most (13 of 16) specimens displayed minimal prominence of nodules (1+ or 2+).

No significant difference was noted in survival from lymphoma between tumors classified as follicular and those classified as follicular and diffuse (Table 4).

### Table 3. Nodular Histiocytic Lymphoma: Degree of Nodularity

<table>
<thead>
<tr>
<th>Nodularity</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>25</td>
<td>3</td>
</tr>
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*Estimated proportion of the lymph node specimen displaying a nodular histologic pattern.

†Estimate of the prominence of nodularity: 4+, very prominent and sharply defined; 1+, vague and very poorly defined.

<table>
<thead>
<tr>
<th>Pattern</th>
<th>All Treatments</th>
<th>Combination Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>CR</td>
</tr>
<tr>
<td>Follicular</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Follicular + diffuse</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>
tumor. However, it must be stressed that all of these patients regardless of the prominence of nodularity were treated with aggressive chemotherapy regimens.

**Pattern of Histologic Progression**

We have previously reported that a significant fraction of nodular lymphomas eventually convert their histology over the course of the disease to a diffuse and/or less differentiated subtype.\(^\text{12}\) Nine of the 16 patients with NH in the present series had a repeat lymph node biopsy and/or a review of lymph node histopathology at autopsy (Table 5). Five patients had repeat lymph node biopsies because of disease progression 2–11 mo after their initial diagnosis. Lymph node histopathology of one of these patients (2) was interpreted as NML. This patient died of lymphoma 9 mo later, but an autopsy was not obtained. The other 4 patients undergoing rebiopsy during the course of their disease all revealed a diffuse and/or less differentiated subtype of lymphoma (2 DUL, 2 DHL). Lymph nodes from 6 patients were examined at autopsy (Table 5). Patient 1, who had been treated with combination chemotherapy following relapse from previous radiotherapy, died of bleomycin pulmonary toxicity and had no residual lymphoma at autopsy. Lymph node examination of the other 5 patients autopsied revealed a diffuse pattern in all. Thus, in this series, the majority of patients originally presenting with NH eventually converted their histology to a more aggressive diffuse lymphoma.

**DISCUSSION**

Nodular histiocytic lymphoma is uncommon, comprising about 3% of our series of patients with non-Hodgkin’s lymphoma. In several other large series of non-Hodgkin’s lymphomas, the prevalence of NH ranged from 0% to 7%.\(^\text{11,13-15}\) The low frequency of NH may explain the paucity of information concerning its natural history, response to treatment, and prognosis.

In general, the nodular lymphomas of the Rappaport classification are thought to be a relatively homogeneous group of disorders characterized by a good response to treatment, indolent course, and thus, a “favorable” prognosis. It is also recognized, however, that although nodular lymphomas respond well to initial treatment and have an indolent natural history, prolonged disease-free survival or cure is uncommon even with combination chemotherapy. This has led to the use by many physicians of less intensive treatment regimens for the “favorable” prognosis lymphomas, since cure of the disease does not seem to be a realistic goal at this time.\(^\text{16}\)

Recent studies suggest that not all nodular subtypes of non-Hodgkin’s lymphomas fit this general pattern of response to treatment, and that subclassification according to the predominant cell type may be important. For instance, we and others have previously reported a high complete remission rate and prolonged disease-free survival in patients with NML treated with intensive chemotherapy.\(^\text{4,17,18}\) These results await confirmation by more prolonged follow-up and additional clinical trials.

The present study of patients with nodular histiocytic lymphoma suggests that this disease exhibits characteristics of other nodular lymphomas as well as diffuse histiocytic lymphoma. Similar to the other nodular lymphomas, and in contrast to diffuse histiocytic lymphoma, NH uncommonly presents with localized disease (PS I or II) at the time of diagnosis.\(^\text{13,19-21}\) More than 80% of the patients in our series presented with advanced stage disease. The slightly lower percentage of advanced disease noted in two other series probably reflects less vigorous staging procedures.\(^\text{13,21}\)

Survival curves that span 22 yr (1953–1975, including all histologies) of evolving treatment approaches can be expected to provide only some general observations regarding prognosis of patients with various types of non-Hodgkin’s lymphoma. However, the survival of patients with NH appears to be intermediate between that of other nodular lymphomas and the more aggressive diffuse histiocytic lymphoma (Fig. 1), a trend that has been observed in previous studies.\(^\text{1,13,21-23}\) Patients with NPDL have an indolent course and favorable prognosis with a median survival from diagnosis of 78 mo. However, prolonged disease-free survival is uncommon in these patients, and a plateau of the tumor mortality curve is not evident. Patients with NML also tend to have an indolent course with a median survival of 55 mo. Patients with DHL have a very aggressive course with a 10-mo
significant proportion (25%) have a very unfavorable subtype of lymphoma, a median survival. Despite the fact that these patients have a very unfavorable subtype of lymphoma, a significant proportion (25% in this series, which includes patients treated by suboptimal therapy in the 1950s and 60s) will have prolonged disease-free survival tantamount to cure. More recent studies suggest that the proportion of patients with DHL remaining disease-free after intensive therapy may be substantially higher than 25%.

Patients with NH also have a more aggressive course than those with other nodular lymphomas. Although the statistical comparisons of these curves by the two-sided generalized Wilcoxon test do not reach significance when NH is compared to NML, the trend is for NH to be more aggressive with a median survival of 31 mo.

The most important observation in the present study, however, is that, similar to DHL, intensive combination chemotherapy may produce durable long-term disease-free survival in patients with NH. All but one of the patients achieving complete remission with combination chemotherapy remain in continuous complete remission without maintenance therapy with a follow-up ranging from 4.5 to more than 11 yr. None of the patients treated initially with various forms of radiation therapy had durable remissions, and all are dead.

The similarity between NH and DHL may also be reflected in the histopathologic findings. The prominence of nodularity was minimal in most of our patients with NH and, in most, large areas of diffuse proliferation were noted. Furthermore, the lymph node histopathology in the majority of patients in whom serial examination was possible changed to either DHL or DUL during the course of the disease. There is now increasing evidence to support the observations of Gall and Mallory, and Rappaport that part of the natural history of nodular lymphomas may be to become more diffuse architecturally and less differentiated cytoplogically with time. Because of the tendency for NH to convert to DHL, and because of the potential in both for prolonged disease-free survival, these two subtypes of lymphoma should be approached therapeutically in a similar fashion with intensive combination chemotherapy for the majority of patients.

REFERENCES

NODULAR HISTIOCYTIC LYMPHOMA


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CK Osborne, L Norton, RC Young, AJ Garvin, RM Simon, CW Berard, S Hubbard and VT Jr DeVita