Central Nervous System Complications in Patients With Diffuse Histiocytic and Undifferentiated Lymphoma: Leukemia Revisited

By Paul A. Bunn, Jr., Philip S. Schein, Peter M. Banks, and Vincent T. DeVita, Jr.

Fifteen of 52 patients (29%) with diffuse histiocytic and undifferentiated pleomorphic lymphoma developed central nervous system (CNS) complications, primarily leptomeningeal lymphoma. Lumbar puncture with cerebrospinal fluid cytology was the most useful test for diagnosis, and for following the response to therapy. Leptomeningitis developed during all stages of the patients' clinical course: at time of diagnosis, during progression of systemic disease, and most importantly as the initial site of relapse within 7 mo of attaining a complete clinical remission. Patients with bone marrow involvement are at high risk for the development of leptomeningeal lymphoma. Pathologic findings suggest that entry into the leptomeninges involves extension from the medullary bone marrow cavity along perforating vessels through dura into the arachnoid space. The leptomeningeal lymphoma has been successfully controlled in all patients receiving intensive central nervous system therapy consisting of a combination of intrathecal drug administration and radiotherapy. The high frequency of this syndrome and the success in its control suggest that a controlled trial of prophylactic CNS therapy be instituted in patients with these histologic types of non-Hodgkin's lymphomas.

Prior to the development of effective chemotherapy, neurologic complications of both leukemias and lymphomas were considered uncommon. A changing natural history for the leukemias was observed as more patients attained a remission and survival was improved. This observation has been particularly apparent for acute lymphocytic leukemia (ALL) where long remissions are associated with infiltration of the meninges in as many as 50% of patients. A similar increase in the incidence of leptomeningeal involvement complicating the myelogenous leukemias has recently been demonstrated. In contrast to the leukemias, less than 5% of patients with malignant lymphoma classified as Hodgkin's disease, follicular lymphoma, lymphosarcoma, or...
reticulum cell sarcoma have been reported to develop neurologic complications.\textsuperscript{4,10} With an increasing use of the Rappaport classification,\textsuperscript{11} the variation in the natural history of subcategories of the non-Hodgkin’s lymphomas has been better appreciated.\textsuperscript{12,13} Three recent studies suggest that there may be an increasing incidence of neurologic complications in diffuse histiocytic lymphoma.\textsuperscript{14,16} We have recently reported an increased disease-free survival in patients with diffuse histiocytic lymphoma (DHL) and diffuse undifferentiated pleomorphic lymphoma (DUL) treated with combination chemotherapy.\textsuperscript{15,17} In these histologic subgroups we observed an apparent increase in the incidence of central nervous system (CNS) complications.\textsuperscript{18} In this report, we present a retrospective analysis of the neurologic complications documented in patients with DHL and DUL.

**MATERIALS AND METHODS**

The clinical courses of 52 patients with a histologic diagnosis of DHL or DUL admitted to the NCI between the years 1965 and 1975 have been reviewed. Patients were staged according to the recommendations of the Ann Arbor Conference.\textsuperscript{19} The standard staging evaluation as reported elsewhere\textsuperscript{13} included percutaneous liver biopsy, bilateral bone marrow biopsies, and peritoneoscopy. Laparotomy was performed only if indicated by the need to clarify an equivocal finding. The initial systemic treatment program depended on the stage and varied over the duration of analysis. Patients with stage I or stage II disease received either radiotherapy alone (eight pa-

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**Table 1. Clinical Course of 15 Patients With CNS Complications**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age</th>
<th>Sex</th>
<th>Initial Clinical Stage</th>
<th>Initial Systemic Therapy*</th>
<th>Time From Diagnosis to Clinical Status</th>
<th>Time From Diagnosis to Positive Marrow (mo)</th>
<th>Time From Diagnosis to CNS Complication (mo)</th>
<th>Clinical Status at Onset of CNS Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>M</td>
<td>IV</td>
<td>BACOP</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>M</td>
<td>IV</td>
<td>BACOP</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>F</td>
<td>IV</td>
<td>C-MOPP</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>M</td>
<td>IV</td>
<td>BACOP</td>
<td>Never documented</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>M</td>
<td>IV</td>
<td>C-MOPP</td>
<td>At diagnosis</td>
<td>61</td>
<td>Clinical remission</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>M</td>
<td>IV</td>
<td>BACOP</td>
<td>At diagnosis</td>
<td>6</td>
<td>Clinical remission</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>F</td>
<td>IV</td>
<td>C-MOPP</td>
<td>At postmortem</td>
<td>6</td>
<td>Clinical remission</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>M</td>
<td>I</td>
<td>TNI</td>
<td>At postmortem</td>
<td>13</td>
<td>Clinical remission</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>F</td>
<td>III</td>
<td>C-MOPP</td>
<td>Never documented</td>
<td>13</td>
<td>Clinical remission</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>F</td>
<td>IV</td>
<td>TBI</td>
<td>At diagnosis</td>
<td>5</td>
<td>Progressive disease</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>M</td>
<td>IV</td>
<td>MOPP</td>
<td>2</td>
<td>3</td>
<td>Progressive disease</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>12</td>
<td>55</td>
<td>F</td>
<td>IV</td>
<td>C-MOPP</td>
<td>14</td>
<td>17</td>
<td>Progressive disease</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>13</td>
<td>70</td>
<td>M</td>
<td>III</td>
<td>C-MOPP</td>
<td>23</td>
<td>24</td>
<td>Progressive disease</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>F</td>
<td>IV</td>
<td>BACOP</td>
<td>15</td>
<td>16</td>
<td>Progressive disease</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>15</td>
<td>43</td>
<td>M</td>
<td>IV</td>
<td>C-MOPP</td>
<td>At postmortem</td>
<td>3.5</td>
<td>Progressive disease</td>
<td>At diagnosis</td>
</tr>
</tbody>
</table>

* Clinical course of 15 patients with CNS complications. CVP\textsuperscript{22}: Cyclophosphamide, 400 mg/sq m po qd × 5 days; vincristine, 1.4 mg/sq m i.v. day 1; prednisone, 100 mg/sq m po qd × 5 days, repeated every 21 days. MOPP\textsuperscript{23}: Nitrogen mustard, 6 mg/sq m i.v. days 1,8; vincristine, 1.4 mg/sq m i.v. days 1,8; Procarbazine, 100 mg/sq m po qd × 14 days; prednisone, 40 mg/sq m po qd × 14 days, repeated every 28 days. C-MOPP\textsuperscript{13}: Same as MOPP with substitution of cyclophosphamide 650 mg/sq m i.v. day 1,8 for nitrogen mustard repeated every 28 days. BACOP\textsuperscript{24}: Adriamycin, 25 mg/sq m i.v. day 1,8; Cytoxan 650, mg/sq m i.v. day 1,8; vincristine, 1.4 mg/sq m i.v. day 1,8; bleomycin, 5 mg/sq m i.v. day 15,22; prednisone, 40 mg/sq m po qd days 15-28, repeated every 28 days. TBI\textsuperscript{20}: Total body irradiation. TNI\textsuperscript{21}: Total nodal irradiation.

* This patient had spinal cord compression.\n† This patient had both spinal cord compression and leptomeningitis.
LEUKEMIA REVISITED

The 40 patients with advanced stages received one of the four combination chemotherapy programs listed in Table I. Patients were considered to have achieved a complete remission when all clinically detectable disease disappeared and did not recur for the duration of treatment.

Diagnostic evaluation of the CNS was performed only if indicated by neurologic symptoms and signs or if circulating lymphoma cells were found in the peripheral blood. Leptomeningeal involvement was documented in all cases by cerebrospinal fluid (CSF) cytology and postmortem findings. CSF cytology was assessed by Papanicolaou-stained, mounted Millipore filter (5 μ) preparations produced by quantitative mixture with 70%, ethanol.

Treatment for lymphomatous involvement of the CNS was not standardized in these patients. Where radiation therapy was employed, a total dose of 3000 R was administered to the cranium and involved spinal roots over a 3-wk period. Where intrathecal drug was used alone or with radiation therapy, methotrexate, 12-15 mg/sq m, followed by leukovorin rescue, or arabinosyl cytosine, 30 mg/sq m, was given twice weekly until cerebrospinal fluid cytology returned to normal. Weekly intrathecal drug treatment was continued until the neurologic signs and symptoms resolved or stabilized, and then was continued indefinitely on a semimonthly or monthly schedule.

RESULTS

The characteristics of the 52 patients in this series are presented in Table 2. The overall incidence of involvement of the CNS by lymphoma was 29% (15 of 52) and included 13 patients with leptomeningitis, one patient with spinal cord compression, and one patient with both complications. The age, sex, and initial treatment of these 15 patients were not different from the others (Table 2). Patients developing a CNS complication were more likely to have advanced disease. Details of the clinical course of these 15 patients are provided in Table 1.

Malignant lymphoma involving the bone marrow was diagnosed in 20 of 52 patients, and 13 of these 20 patients (65%) were in the group that developed leptomeningitis. Only one patient of the 14 with lymphomatous leptomeningitis had no bone marrow involvement. The bone marrow involvement preceded or occurred at the same time as the leptomeningitis in 10 of these 13 cases and was documented at postmortem in the remaining three.

In general, the signs and symptoms associated with CNS lymphoma were similar to leukemic involvement of the CNS. Alterations in mental status ranging from confusion, somnolence, or personality change, to marked dementia and coma were the most common and pronounced symptoms in patients with leptomeningitis (10 of 14). These symptoms frequently developed abruptly over a period of a few days. The majority (six of ten) of these patients also had extensor plantar responses. There were no instances of focal or generalized seizure

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**Table 2. Patient Characteristics**

<table>
<thead>
<tr>
<th>Study</th>
<th>CNS Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (DHL/DUL)</td>
<td>52 (47/5) 15 (13/2)</td>
</tr>
<tr>
<td>Age mean (range)</td>
<td>47 (21-75) 45 (21-70)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>33/19 10/5</td>
</tr>
<tr>
<td>Initial pathologic stage: I + II</td>
<td>12 1</td>
</tr>
<tr>
<td>III + IV</td>
<td>40 14</td>
</tr>
<tr>
<td>Complete remission</td>
<td>25/52 (48%)</td>
</tr>
<tr>
<td>Relapses</td>
<td>9/25</td>
</tr>
<tr>
<td>Primary CNS relapse</td>
<td>5/9</td>
</tr>
</tbody>
</table>
disorders. Nausea, vomiting, papilledema, or signs of meningeal irritation were not observed.

Seven of the 14 patients with leptomeningitis had signs of cranial nerve involvement, and disorders of multiple cranial nerves were common. Cranial nerves III, IV, and VI were most frequently involved (four patients), followed by cranial nerve VII and XII in two patients each, and cranial nerve V in a single patient. In five patients there were symptoms and signs of focal sensory loss, weakness, and hyporeflexia which was considered to be related to lymphomatous involvement of a specific spinal root.

The CSF cytology was positive in 100%, (ten of ten) of the patients with leptomeningitis in whom cytologic studies were performed. However, in two of these ten cases the CSF white blood cell count was less than 10 cells per μl, and the diagnosis was made on a morphologic basis. Typical malignant cells in the CSF are illustrated in Fig. 1. Abnormalities of CSF glucose (low in 7 of 13 instances) and CSF protein (elevated in 10 of 13 instances) were common. The opening pressure was elevated (>160 mm H₂O) in only three of the ten patients in whom it was recorded, and in only one case was the opening pressure recorded as greater than 200 mm H₂O. Skull roentgenograms were abnormal in only 2 of 11 cases, and in both instances lytic lesions were demonstrated. Brain scans were abnormal in three of seven patients. All four cases in which electroencephalograms were performed revealed diffuse nonspecific abnormalities. In addition,
two of the four cases also had EEG findings suggesting the presence of mass lesions in an area corresponding to a brain scan defect.

Primary treatment with combination chemotherapy resulted in complete clinical remission of systemic disease in 25 of the 52 patients (Table 2). Nine of these patients later relapsed, all within 9 mo of completion of therapy. The CNS was the primary site of relapse in five of these nine cases. Reappearance of tumor elsewhere occurred later or was diagnosed at postmortem in all of these five primary CNS relapses.

Neurologic complications in the 15 patients were diagnosed during all stages in the patients' clinical course (Table 1); (1) at the time of initial staging evaluation (four patients), (2) following the development of complete remission after therapy had been discontinued (five patients), and (3) during progressive systemic disease (six patients).

Of the 14 patients with lymphomatous leptomeningitis, 7 had complete disappearance of the malignant CSF cells with irradiation and intrathecal drug, or
intrathecal drug alone. In these patients the beneficial effects were noted within 3 wk (three to six doses of intrathecal drug). Although all seven of these patients who responded to CNS treatment have since died, none of the deaths were attributed to CNS lymphoma; six died of progressive systemic tumor unresponsive to systemic treatment, and one from infection related to drug induced marrow aplasia. Six of these seven patients came to autopsy; three had no residual evidence of CNS lymphoma, and in the remaining three CNS therapy was discontinued because of imminent death from systemic overgrowth of tumor. Six other patients died of progressive systemic disease before treatment for the leptomeningitis could be instituted (three cases) or completed (three cases). The remaining patient was incorrectly diagnosed as having a cerebrovascular accident, and a postmortem revealed CNS lymphoma.

Pathologic changes at autopsy (Table 3) were similar to those previously described in patients with ALL. The dura and/or arachnoid, the most superficial CNS structures, were involved in all cases. Deep lymphomatous infiltration into cerebral substance was found in five of the nine cases, and all had co-existing infiltration of the arachnoid.

The cerebral lymphoma followed a conspicuous pattern of infiltration along perivascular (Virchow-Robin) spaces in continuity with densely infiltrated leptomeninges (Fig. 2). There were no instances of isolated foci of tumor within the cerebral substances such as is commonly found with hematogenous dissemination of carcinoma.

**DISCUSSION**

The 27% incidence of leptomeningeal lymphoma in patients with DHL and DUL is significantly higher than any previously reported series. This high frequency of leptomeningitis appears to be related to two factors: (1) The increased survival of these patients following intensive treatment may have allowed for the development of this complication, in analogy with both ALL and AML. (2) Patients with DHL and DUL are more susceptible to this complication than are other histologic subgroups, a fact not previously appreciated.

The Rappaport classification has led to new appreciation of differences in the natural history of the non-Hodgkin's lymphomas. In previous reports less than 5% of patients classified as giant follicular lymphoma, lymphosarcoma, or reticulum cell sarcoma were reported to have developed leptomeningeal lymphoma. The recent studies of Gendleman et al. and Olsen et al. suggested a rising incidence of lymphomatous leptomeningitis. Unfortunately, the older generic classification was used, and the incidence could not be determined as the total number of patients was not provided. Griffin et al. found 21 cases of lymphomatous leptomeningitis in a 5-yr period at Stanford University, 18 of which had a histologic diagnosis of DHL or DUL, and none had a nodular lymphoma. This finding suggested that these histologic subgroups were more susceptible to this complication; unfortunately the total number of patients from which the 18 were selected was not provided.

The newer intensive treatment regimens may have led to CNS complications by controlling systemic disease but not affecting the CNS "sanctuary" and thus allowing CNS relapse from remission. One-third of the CNS complications in
the present series occurred in patients in remission, all within 7 mo after completion of therapy.

Gendelman et al. previously reported an increased incidence of CNS lymphoma in patients with preceding bone marrow involvement. Similarly, Griffin et al. found bone marrow involvement in 100% of their autopsied cases with lymphomatous leptomeningitis. The results of the present series strongly re-emphasized the close correlation of bone marrow and CNS involvement. The majority of patients (65%) with bone marrow involvement will develop leptomeningeal lymphoma, and nearly all patients with this complication can be shown to have had preceding bone marrow lymphoma. The incidence of bone marrow involvement in patients with DHL at initial staging is significantly lower than in patients with nodular lymphomas (approximately 15% versus 40%). Nevertheless, lymphomatous leptomeningitis appears to be rare in patients with nodular lymphomas. The reason for this discrepancy in correlation between bone marrow and leptomeningeal infiltration in the nodular lymphomas is unexplained. The pathologic features of these lymphomas when they involve the CNS and the consistent association of bone marrow tumor with CNS disease suggest that malignant lymphoma cells spread directly from the medullary cavity along tissue planes (perforating vessels and nerves), through dura and into the arachnoid space, which is in direct continuity with the perivascular Virchow-Robin space. This method of spread is similar to that reported by Thomas in acute leukemia.

The 20% incidence of CNS relapse in our patients achieving a complete remission is high and accounted for five of the nine relapses. Because of the propensity for lymphomatous involvement of multiple areas of the neuraxis and the free flow of malignant cells in the CSF, therapy must be directed to all of these areas. A combination of cranial irradiation and intrathecal drug administration provided adequate control of the lymphomatous leptomeningitis in all our patients with established involvement. Prophylactic treatment of the CNS has not been routinely employed in patients with lymphoma. Because of the high CNS relapse rate in patients with the histologic subgroups of DHL and DUL and because intensive CNS therapy can control established leptomeningeal lymphomas, prospective studies to test the value of prophylactic CNS therapy in those patients obtaining remission of systemic disease appear warranted.

ACKNOWLEDGMENT

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