Primary central nervous system lymphomas: natural history and response to radiation therapy in 55 patients with acquired immunodeficiency syndrome

JAMES E. BAUMGARTNER, M.D., JACOB R. RACHLIN, M.D., PH.D., JAY H. BECKSTEAD, M.D., TIMOTHY C. MEKKER, M.D., ROBERT M. LEVY, M.D., PH.D., WILLIAM M. WAR, M.D., AND MARK L. ROSENBLUM, M.D.

Departments of Neurological Surgery, Pathology, Laboratory Medicine, Radiation Oncology, and Pediatrics, School of Medicine, University of California, San Francisco, California

The incidence of primary central nervous system (CNS) lymphoma has increased rapidly in patients with acquired immunodeficiency syndrome (AIDS) and is predicted to exceed 1800 cases annually by 1991. To characterize the natural history and response to radiation therapy (RT) of these lesions, the authors have reviewed the clinical histories of 55 AIDS patients with biopsy-proven primary CNS lymphomas. The tumors responded both clinically and radiologically to whole-brain RT consisting of 4000 rad in 267-rad fractions over 3 weeks or an equivalent neuroret dose. The mean duration of survival from the appearance of symptoms consistent with the mass lesion was significantly greater in patients who received RT than in those who did not (42 vs. 134 days, p < 0.5; median 27 vs. 119 days). Autopsy findings showed that patients who did not receive RT died from tumor progression, whereas those who completed RT died of opportunistic infections. Patients with AIDS who are suspected of having primary CNS lymphoma should therefore immediately undergo biopsy and, if the diagnosis is confirmed, whole-brain RT. With early diagnosis and treatment, these tumors respond to, and patients benefit from, RT. Survival of such patients may in future be prolonged by more effective treatments for systemic opportunistic infections.

Key Words • lymphoma • acquired immunodeficiency syndrome • radiation therapy • central nervous system

The incidence of primary central nervous system (CNS) lymphoma, previously a rare disease accounting for 1% to 1.5% of all primary brain tumors, has increased rapidly over the past 10 years. Until the early 1980's, renal and cardiac transplant patients, who received immunosuppressant medication, were at highest risk for these tumors; since then, there has been a remarkable increase in primary CNS lymphomas associated with acquired immunodeficiency syndrome (AIDS). In a recent review of 1286 adults with AIDS, primary CNS lymphoma was found in eight patients at presentation (0.6%) and developed subsequently in 25 (1.9%). Primary CNS lymphoma is the second most frequent CNS mass lesion in adults with AIDS and the most frequent in children with AIDS (3%). Using these data and a predictive model developed by the Centers for Disease Control, we estimate that in 1986 the annual incidence of AIDS-associated primary lymphomas in the United States surpassed that of primary CNS lymphomas not related to AIDS (266 vs. 225 cases). By 1991, AIDS-related primary lymphomas will be more common (1848 cases) than low-grade astrocytomas (1500 cases) and almost as common as meningiomas (2250 cases).

Descriptions of the irradiation responsiveness of primary CNS lymphoma in AIDS patients are limited to case reports and small series. Most of the tumors were diagnosed at autopsy or shortly before the patient's death. To elucidate the natural history of these tumors and to assess their response to radiation therapy (RT), we reviewed the course of 55 AIDS patients with primary CNS lymphomas.

Clinical Material and Methods

Study Population

The study population consisted of all patients with a diagnosis of AIDS and pathologically proven CNS lym-
Primary CNS lymphomas in AIDS patients

who were treated at five San Francisco hospitals from March, 1982, through February, 1989. Patients were identified from the pathology logs of the San Francisco General, Pacific-Presbyterian, and Moffit-Long Hospitals (12 cases) or at the time of diagnostic surgical biopsy (43 cases). The signs and symptoms, tumor location and pathology, concurrent illnesses, and the response to treatment were reviewed.

Surgical Methods

Diagnostic surgical intervention was carried out in 45 cases (51 procedures). This consisted of open craniotomy (16 procedures) or stereotactic needle biopsy guided by computerized tomography (CT) (26 procedures) or by ultrasound (nine procedures).

Pathological Examination

Frozen, plastic-, and paraffin-embedded sections of each surgical specimen were analyzed microscopically. Autopsy specimens were embedded in paraffin and, when available, in plastic for microscopic analysis. All specimens were reviewed by one of the authors (J.H.B.) to confirm diagnosis. The working formulation for clinical use of the National Cancer Institute was used to classify the tumors.

Treatment

Twenty patients completed an RT protocol consisting of 4000 rad of whole-brain radiation in 267-rad fractions over 3 weeks; three patients who started the protocol following delays of 4, 6, and 8 weeks after biopsy deteriorated early and withdrew after receiving 600, 900, and 1200 rad. Nine patients received an equivalent neurorot dose of whole-brain RT (3000 rad in 300-rad fractions over 2 weeks or 5400 rad in 180-rad fractions over 6 weeks), and three patients received whole-brain RT that was not considered equivalent to the RT protocol (2130 rad in 10 fractions over 10 days, 4800 rad in 34 fractions over 7 weeks, and 3060 rad in 18 fractions over 4 weeks). Of 17 patients who had symptoms consistent with a CNS mass lesion, nine refused RT after surgical diagnosis and eight either refused or were not offered biopsy. In three patients, primary lymphoma was identified incidentally at autopsy.

All patients who underwent RT received corticosteroids (usually beginning at the time of surgery and continuing at least through the end of RT) at doses equivalent to 4 mg of dexamethasone per day. Ten of 20 patients who did not receive RT were given corticosteroids; the dosage and duration of treatment varied greatly. Whenever possible, corticosteroids were tapered within 1 to 4 weeks after completion of RT. Three patients received intravenous high-dose methotrexate, and one patient received intravenous bleomycin.

Response to Treatment

A clinical response was defined as stabilization or improvement in neurological function after completion of the RT protocol on a stable or decreasing dose of corticosteroids. A clinical failure was defined as deterioration in neurological function after completion of the RT protocol.

The radiological response to RT was determined by measuring tumor size on CT scans or magnetic resonance (MR) images within 1 month after completion of the RT protocol. A complete response was defined as more than a 95% reduction in tumor size compared with pretreatment CT scans, a partial response as a reduction of more than 25% and less than 95%, stable disease as a reduction or enlargement of 25% or less, and treatment failure as an increase of more than 25%.

Survival Data

The duration of survival was calculated from the time of the change in neurological status that led to preoperative evaluation or, if no premortem diagnosis was made, from the time of a discrete change in neurological status consistent with CNS lymphoma diagnosed at autopsy. Two patients whose tumors were diagnosed incidentally at autopsy had no symptoms of CNS lymphoma; one additional patient with biopsy-proven toxoplasmosis who had a partial response to anti-toxoplasma therapy was found to have lymphoma at autopsy. These three patients and the three patients who failed to complete the RT protocol were excluded from survival calculations.

Statistical Analysis

The statistical significance of differences in the duration of survival was determined using the paired t-test.

Results

Clinical Presentation

Fifty-three of the 55 patients were homosexual, and two, one of whom was bisexual, had a history of intravenous drug abuse. The mean age was 35 years. In nine cases (16%), primary CNS lymphoma was the first manifestation of AIDS. Ten patients (18%) had Kaposi’s sarcoma, and 42 (76%) had other opportunistic infections, including Pneumocystis pneumonia (15 cases), cryptococcal meningitis (four cases), thrush (seven cases), cytomegalovirus retinitis (five cases), genital or rectal herpes (six cases), toxoplasmosis (seven cases), Mycobacterium avium-intracellulare (two cases), histoplasmosis (one case), and tuberculosis (one case). None of the patients had diffuse lymphadenopathy on initial physical examination or on the staging examination before beginning RT.

The neurological symptoms are summarized in Table 1. Computerized tomography scans obtained after administration of a double dose of intravenous contrast material showed unifocal material in 37% of patients and multifocal lesions in 63% of patients. No spinal cord lesions were identified by initial CT or MR studies.
TABLE 1
Presenting symptoms in 55 patients with primary central nervous system lymphomas

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>confusion, memory loss, lethargy</td>
<td>29</td>
</tr>
<tr>
<td>hemiparesis, dysphasia</td>
<td>17</td>
</tr>
<tr>
<td>seizures</td>
<td>11</td>
</tr>
<tr>
<td>cranial nerve deficit</td>
<td>10</td>
</tr>
</tbody>
</table>

TABLE 2
Diagnostic findings of 51 surgical procedures in 45 patients with primary CNS lymphomas

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Total Procedures</th>
<th>Diagnostic No.</th>
<th>Non diagnostic No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>stereotactic biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT-guided</td>
<td>26</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>ultrasound-guided</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>craniotomy</td>
<td>16</td>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

* CNS = central nervous system; CT = computerized tomography.

Surgical Findings
Fifty-one surgical procedures were performed on 45 patients (Table 2). There were no operative deaths or surgical morbidity. Two patients died within 1 week after surgery, but at autopsy the cause of death was determined to be intercurrent opportunistic infection. In three of four cases in which CT-guided stereotactic biopsies were negative, repeat CT-guided biopsies yielded diagnostic tissue; the fourth patient underwent an open biopsy, which was also diagnostic. Both nondiagnostic open craniotomies were repeated and diagnostic results were obtained.

Pathological Findings
The pathological findings are summarized in Table 3. All patients had high-grade lymphomas. In two cases lymphoma and toxoplasmosis and in one case lymphoma and *M. avium-intracellulare* were found in the same biopsy specimen.

TABLE 3
Pathological findings in 55 primary central nervous system lymphomas

<table>
<thead>
<tr>
<th>Type of Lymphoma</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>small-cell, noncleaved</td>
<td>18</td>
</tr>
<tr>
<td>large-cell, immunoblastic</td>
<td>17</td>
</tr>
<tr>
<td>large-cell</td>
<td>7</td>
</tr>
<tr>
<td>lymphoma not otherwise specified</td>
<td>10</td>
</tr>
<tr>
<td>lymphoma + toxoplasmosis</td>
<td>2</td>
</tr>
<tr>
<td>lymphoma + <em>Mycobacterium avium-intracellulare</em></td>
<td>1</td>
</tr>
</tbody>
</table>

Response to Treatment
The response to the RT protocol or its equivalent is summarized in Table 4. Clinically, 22 (76%) of 29 patients improved and four (14%) stabilized. Only three (10%) of 29 patients deteriorated neurologically. Radiological imaging studies were obtained after RT in 23 patients. Sixteen patients (69%) had a complete or partial response, and five (22%) had stable disease (Figs. 1 and 2).

Survival Data
The survival data are summarized in Table 5. The mean duration of survival was 42 days in patients who did not receive RT, 99 days in those who completed nonprotocol RT, and 134 days in those who completed the RT protocol (p < 0.05 vs. untreated group). Among untreated patients, only 20% lived 3 months and none lived 6 months, whereas among the 29 adequately irradiated patients, 65% lived for 3 months, 21% for 6 months, and 10% for 9 months. Six (21%) of the 29 irradiated patients are still alive. The three patients who
Primary CNS lymphomas in AIDS patients

FIG. 1. Computerized tomography scans with contrast enhancement obtained before (left) and after (right) the radiation therapy protocol in a patient with right frontal and right basal ganglia lesions. A complete response to treatment is demonstrated.

TABLE 6

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Cases</th>
<th>CNS Lymphoma</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>no RT</td>
<td>13†</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>RT protocol or equivalent</td>
<td>8</td>
<td>1‡</td>
<td>7</td>
</tr>
</tbody>
</table>

* CNS = central nervous system; RT = radiation therapy.
† Included two patients with incomplete RT protocol (600 and 900 rad).
‡ This patient had a complete response to the RT protocol but died of an intramedullary high-grade lymphoma of the high cervical spine outside the initial field of radiation.

received high-dose methotrexate completed the RT protocol and survived 245, 122, and 380+ days.

Statistical analysis of the survival data according to presenting symptoms, unifocal versus multifocal lesions on initial CT scans, and tumor histology showed no statistically significant differences in the duration of survival between these patient groups.

Autopsy Findings

Twenty-one of the 55 patients came to autopsy: 13 untreated patients and eight patients who completed the RT protocol (Table 6). All 13 patients had multifocal tumors; 10 (77%) died of tumor progression, and three died of other opportunistic infections. None of the eight patients who completed the RT protocol died of tumor progression. Two had residual multifocal primary CNS lymphoma but died of other opportunistic infections. Two with biopsy-proven primary CNS lymphoma had no residual lymphoma and died of Pneumocystis pneumonia. None of these 21 patients had diffuse lymphadenopathy and no occult systemic lymphomas were discovered. No lymphomatous involvement of the meninges was found unless the dura covered a focus of lymphoma.

Discussion

Most patients with AIDS-associated primary CNS lymphoma have multifocal mass lesions that are identified by CT scans and diagnosed by surgical biopsy after empirical therapy for toxoplasmosis fails. The presenting symptoms can be global or focal. Given the debilitated state of these patients, stereotactic biopsy procedures, with their low morbidity and mortality rates, are favored over craniotomy. Our autopsy data suggest that three-fourths of untreated patients die of rapid, multifocal tumor growth within 1 to 1½ months after presentation with primary CNS lymphoma. In contrast, patients treated with whole-brain RT survived an average of 4 to 4½ months and usually died of
opportunist infections rather than tumor progression. Delay in starting RT reduces the clinical and radiological response and duration of survival. The outcome cannot be predicted from the clinical presentation and therefore all patients with AIDS-related primary CNS lymphoma should undergo maximally tolerated whole-brain RT.

Among AIDS patients, the clinical presentation of primary CNS lymphoma is markedly different from that of peripheral non-Hodgkin’s lymphoma. 1–5,7,10,11,15 Ziegler, et al. 14 found diffuse lymphadenopathy in 40% of patients with peripheral non-Hodgkin’s lymphoma. Generalized lymphadenopathy was conspicuously absent in our series. Recent molecular biological studies by Meeker and coworkers (TC Meeker, L Kaplan, B Herndier, et al.: unpublished data) have shown differences between peripheral and primary CNS lymphomas in AIDS patients despite their histopathological similarities. The six primary CNS lymphomas studied by Meeker, et al., all from patients in the present study, were large-cell, immunoblastic lymphomas that were monoclonal, positive for Epstein-Barr virus, and did not show detectable c-myc rearrangement. In contrast, peripheral non-Hodgkin’s lymphomas were monoclonal in approximately 50% of cases, showed detectable c-myc rearrangement in 36%, and were positive for Epstein-Barr virus in 50%. These observations suggest pathogenetic differences between these two types of CNS lymphomas.

A prospective study with better documentation of each patient’s condition at the various stages of treatment would improve our understanding of the natural history of AIDS-associated primary CNS lymphoma. Since the number of autopsies performed on patients who die of AIDS has been decreasing, it is difficult to determine if estimates of the prevalence of primary CNS lymphoma determined at autopsy earlier in the epidemic 9 remain accurate. It is also difficult to know how many patients die with undiagnosed tumors. In one study, AIDS-related disease not suspected clinically was found at autopsy in 75 of 101 patients. 13 In our study, patients with primary CNS lymphoma who completed the RT protocol died from systemic AIDS-related disease rather than tumor progression. Better diagnosis and treatment of systemic opportunistic infection might improve survival in this patient population, as would more effective treatment for human immunodeficiency virus infection. The marked sensitivity to radiation shown by AIDS-associated primary CNS lymphoma suggests that the pessimism often associated with the treatment of AIDS patients with CNS mass lesions might not be appropriate. Further study of the pathophysiology and treatment of this increasingly frequent tumor is necessary.

Conclusions

The frequency of AIDS-associated primary CNS lymphoma is rapidly increasing in adults and children.
Primary CNS lymphomas in AIDS patients


———

Manuscript received September 12, 1989.
Accepted in final form January 24, 1990.
This work was supported in part by Grants CA-13525 and CA-31882 from the National Cancer Institute, by a grant from the Veterans Administration, and by a Junior Faculty Research Award from the American Cancer Society to Dr. Meeker.

Address reprint requests to: James E. Baumgartner, M.D., Department of Neurological Surgery, Editorial Office, 1360 Ninth Avenue, Suite 210, San Francisco, California 94122.