Primary central nervous system lymphoma

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A retrospective analysis of 21 cases of primary central nervous system (CNS) lymphoma is reported. All patients presented with a solitary mass in the supratentorial region. None had previously received immunosuppressive therapy. Neuroradiological studies included technetium-99m-pertechnetate brain scanning in eight cases, cerebral arteriography in all 21 cases, and computerized tomography (CT) in 14 cases. The characteristic features were increased uptake in brain scans, mass effect in arteriograms, and marked contrast enhancement on CT scans. Abnormal tumor vessels were occasionally seen on arteriography, and subtraction films were usually required to appreciate tumor stain. All patients underwent craniotomy, and histological studies of the tumors showed a diffuse type of lymphoma in all cases. Immunoglobulin testing was performed in 19 cases and a monoclonal spike was verified in 10, suggesting a B cell origin. All patients were followed until their death except one who was still alive 12 months from onset of symptoms. Therapy included subtotal resection in all 21 cases, whole-brain irradiation in six cases, chemotherapy in two cases, and a combination of whole-brain irradiation and chemotherapy in nine cases. Three different forms of chemotherapy were used. The results suggest that chemotherapy is an important addition to subtotal resection and whole-brain irradiation in the treatment of primary CNS lymphoma.

KEY WORDS • lymphoma • immunoglobulin • craniotomy • irradiation • chemotherapy • central nervous system tumor

LYMPHOMA of the central nervous system (CNS) secondary to systemic lymphoma is more common than primary CNS lymphoma. In 1947, Sparling, et al., reported 19 cases of lymphoma involving the CNS among 118 cases of systemic lymphoma. The majority of secondary lymphomas involve meningeal, perivascular, and spinal epidural areas; however, Jellinger and Radaszkiewicz found an isolated solid mass lesion in the brain in 7% of the cases of secondary CNS lymphomas they found in a review of 145 consecutive autopsy cases of systemic lymphoma. Primary CNS lymphoma has been designated by a variety of terms, including “microglioma” and “reticulum-cell sarcoma.” It is a rare disorder, representing only 0.85% to 1.5% of intracranial neoplasms. There is a surprisingly high incidence, however, in patients receiving immunosuppressive therapy for renal transplantation, systemic lupus erythematosus, and other conditions. In addition, Pattengale, et al., reported a case with a selective immunodeficiency possibly related to the Epstein-Barr virus.

During the period from 1971 to 1983, 21 patients with primary CNS lymphoma were treated at Okayama University Medical School and affiliated hospitals. We have reviewed these cases retrospectively in order to study the clinical, neuroradiological, and histological features, and the results of several treatment modalities.

Summary of Cases

Clinical Material

The clinical and neuroradiological data were obtained from the patients' medical records. All of the patients presented with symptoms and signs referable to a solitary mass of the supratentorial region of the CNS. None had previously received immunosuppressive therapy. All patients underwent subtotal resection of the tumor via a craniotomy, and histological diagnosis of primary CNS lymphoma was made from the surgical specimens. Neuroradiological study included technetium-99m (99mTc)-pertechnetate brain scanning, cerebral arteriography, and computerized tomography (CT) scanning. Immunoglobulin studies with immunofluorescence and/or immunoperoxidase techniques were performed in 19 cases. Fresh and/or paraffin-embedded sections were treated with rabbit antiserum specific for human immunoglobulins (anti-gamma and anti-mu of heavy chains, and anti-kappa and anti-lambda of light chains) in order to look for cell surface
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TABLE 1
Clinical summary of 21 cases of primary central nervous system lymphoma*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Tumor Location</th>
<th>Irradiation (rads)</th>
<th>Chemotherapy</th>
<th>Survival Time (mos)</th>
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<td>1</td>
<td>51, F</td>
<td>lt frontal lobe</td>
<td>—</td>
<td>—</td>
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<td></td>
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<tr>
<td>2</td>
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<td>—</td>
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<tr>
<td>3</td>
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<td>—</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
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<td>8</td>
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<td>—</td>
<td>6</td>
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<td>CHOP</td>
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<td>13</td>
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<td>VEMP</td>
<td>12</td>
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<td>17</td>
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<td>5200</td>
<td>ACNU</td>
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<td>ACNU</td>
<td>28</td>
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<td>4000</td>
<td>CHOP</td>
<td>15</td>
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<td>CHOP</td>
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<tr>
<td>21</td>
<td>66, M</td>
<td>bioccipital lobes</td>
<td>4000</td>
<td>CHOP</td>
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* All patients underwent subtotal tumor resection. For a description of the chemotherapy combinations see text.

or cytoplasmic immunoglobulins. Four different forms of treatment were undertaken: 1) subtotal resection of the tumor only; 2) subtotal resection and irradiation; 3) subtotal resection and chemotherapy; and 4) subtotal resection, irradiation, and chemotherapy. All patients except one were followed until their death; the exception (Case 21) was still alive at the end of the study.

Age and sex, tumor location, treatment, and survival time in this series are summarized in Table 1. The age at onset ranged from 5 to 68 years with a mean age of 50 years. There were 11 males and 10 females. The most common site of involvement was the frontal lobe, followed by the temporal lobe. All patients presented with the symptoms and signs of focal neurological deficits and/or increased intracranial pressure. Neuro-radiological studies included brain scanning in eight patients, cerebral arteriography in 21, and CT scanning in 14. A characteristic feature seen on the brain scans was increased uptake at the site of the tumor. All patients showed mass effect on cerebral arteriography, with displacement and stretching of the intracranial vessels. The presence of abnormal tumor vessels was seen in some cases. Tumor stain was not clear in most cases, and subtraction films were usually required to appreciate it (Fig. 1). The plain CT scans demonstrated an isodense or a slightly high-density mass surrounded by irregular low density (Fig. 2 left). Following the intravenous administration of contrast material, the mass was markedly enhanced in all cases (Fig. 2 right).

Histological examination showed a diffuse type of lymphoma without nodular or follicular formation (Fig. 3). Dedifferentiation, such as undifferentiated, histio-

Fig. 1. Case 9. Left carotid subtraction angiogram, lateral projection, demonstrating a large homogeneous tumor stain (arrows).

Fig. 2. Case 9. Plain computerized tomography (CT) scan (left) demonstrating a slightly high-density mass surrounded by an area of low density. Scan after an administration of contrast material (right) demonstrating marked enhancement of the mass.

Fig. 3. Case 9. Photomicrograph of the tumor demonstrating a diffuse type of lymphoma. H & E, x 150.
cytic, mixed, lymphocytic, or lymphoblastic cell types (as classified in the Rappaport system\textsuperscript{22}) was not definitely identified. Immunohistological globulin studies were performed in 19 patients (Table 2), of whom 11 demonstrated positive staining for heavy chains of immunoglobulin (Ig) and eight were negative. In the 11 positive cases, IgG was positive in 10 cases (Fig. 4 upper left), IgM in nine cases (Fig. 4 upper right), and both IgG and IgM were positive in eight cases. In 10 of the 11 positive-staining cases, only kappa light chains were positive in seven cases and only lambda light chains in three cases (Fig. 4 lower), demonstrating a monoclonal spike. In one case (Case 19) both kappa and lambda light chains stained positively in the majority of the tumor cells.

Treatment and survival time is summarized in Table 1. Subtotal resection was the only treatment in four cases (Cases 1 to 4), subtotal resection and irradiation were performed in six cases (Cases 5 to 10), subtotal resection and chemotherapy in two cases (Cases 11 and 12), and subtotal resection, irradiation, and chemotherapy in nine cases (Cases 13 to 21). The survival time was calculated from the onset of symptoms to death or to the end of the study, and ranged from 5 months to 3 years and 2 months (median 15.3 months). Irradiation was to the whole brain in all cases so treated, and the dose ranged from 3900 to 6000 rads (median 4450 rads). Three forms of chemotherapy were used: CHOP (cyclophosphamide 750 mg/sq m intravenously, Adriamycin (doxorubicin) 50 mg/sq m intravenously, Oncovin (vincristine) 1.4 mg/sq m intravenously, and prednisone 25 mg/6 hrs by mouth); VENP or VEMP (vincristine 0.02 mg/kg intravenously, cyclophosphamide 1.0 mg/kg daily by mouth, procarbazine (Natulan) 1.5 to 3.0 mg/kg daily by mouth or 6-mercaptopurine 1.0 mg/kg daily by mouth, and prednisolone 0.6 to 0.8 mg/kg daily by mouth); and ACNU (1-(4-amino-2-methylpyrimidine-5-yl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride). The dose of each agent in the two combinations of chemotherapy was a little different for each patient: ACNU was given at a dose of 2 mg/kg intravenously once a week for 3 consecutive weeks, in conjunction with 5-fluorouracil, 10 mg/kg intravenously five times weekly, and prednisolone, 0.6 to 0.8 mg/kg daily by mouth. The chemotherapy started after craniotomy and the course was repeated while the patient’s general condition permitted. When the tumor recurred intracranially, the patients were treated with chemotherapy only. Therefore, the number of courses of chemotherapy was different for each patient. During the terminal stage, other types of chemotherapeutic agents were administered to some patients, but were not considered as part of the chemotherapy in this series.

The median survival time was 5.5 months in the four patients treated with subtotal resection only, and 13.5 months in the six patients treated with subtotal resection and irradiation. The two patients treated with subtotal resection and CHOP (Cases 11 and 12) survived 1 year 8 months and 3 years 2 months, respectively. The survival time in the four patients treated with subtotal resection, irradiation, and VEMP or VEMP (Cases 13 to 16) ranged from 5 months to 1 year 3 months (mean 10.7 months). The two patients treated with subtotal resection, irradiation, and ACNU (Cases 17 and 18) survived 2 years 5 months and 2 years 4 months, respectively. Of the three patients who received subtotal resection, irradiation, and CHOP (Cases 19, 20, and 21), two (Cases 19 and 20) survived 1 year 3 months and 3 years 2 months, respectively, and the third (Case 21) was alive and well 12 months after the onset of symptoms.

**Discussion**

Because of the rarity of the disease, no large series of primary CNS lymphoma have been reported. In order to study clinical symptoms and signs, Helle, et al.,\textsuperscript{9} reviewed 15 published series comprising a total of 400 patients. They found a male predominance, an increased incidence in the sixth decade of life, and a preferential site in the frontal lobe. The most common presenting symptoms were headache, nausea, vomiting, and mental changes, and the most common signs were hemiparesis and papilledema. The clinical features in our 21 cases were similar, and were not pathognomonic to primary CNS lymphoma.

A \textsuperscript{99m}Tc-pertechnetate brain scan was performed in eight cases before CT was introduced in our hospitals, and increased uptake at the site of the tumor was seen in all cases. The common arteriographic finding was mass effect with displacement and stretching of the vessels. The presence of abnormal tumor vessels was
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Occasionally observed. Leeds, et al., 15 emphasized focal changes in the blood vessel walls visible on serial magnification angiograms. As Helle, et al., 7 reported, it was difficult to appreciate tumor stain on regular arteriographic films, and this feature was usually seen only on subtraction films (Fig. 1). The CT findings were characteristic, as emphasized by Enzmann, et al., 6 The mass seen on plain CT scans was usually isodense or slightly hyperdense and was surrounded by an irregular low-density area. Marked enhancement was always observed following the intravenous administration of contrast medium (Fig. 2). The limited vascular changes on cerebral arteriograms and the contrast enhancement on CT scans was proposed by Tallroth, et al., 31 to be secondary to lymphoma cells growing along perivascular tissues and into the vessel walls, narrowing but not destroying the vessels while disturbing the blood-brain barrier. These features were considered highly suggestive of a diagnosis of primary CNS lymphoma. Berger, et al., 1 however, reported similar features in patients with primary cerebral neuroblastoma.

In addition to the Rappaport system, a number of methods of classifying systemic lymphoma have been proposed including the latest working formulation for clinical use derived from a National Cancer Institute study 22 but none have achieved general acceptance. Henry, et al., 10 examined 83 primary CNS lymphomas and concluded that their histological patterns were analogous to those seen in malignant lymphomas arising in the reticuloendothelial system of other organs. Letendre, et al., 16 and Helle, et al., 9 classified their cases of primary CNS lymphoma according to the Rappaport system and found a predominance of the diffuse type. In our series, all 21 cases showed a diffuse pattern.

A number of immunohistological studies of systemic lymphoma have been performed in order to classify the origin of tumor cells. 3 It was found that the majority of systemic lymphomas were of the B cell type, with a small number of T cell or null cell types. On the other hand, only a few immunohistological studies have been reported in primary CNS lymphoma. Varadachari, et al., 36 observed B lymphocyte membrane markers on a histiocytic lymphoma. Taylor, et al., 34 observed definite staining of cytoplasmic immunoglobin in 13 of 24 cases of primary CNS lymphoma, and verified a monoclonal spike in eight of the 13 cases. Houthoff, et al., 12 reported similar findings. Of our 19 cases with immunoglobulin testing, a monoclonal spike was verified in 10, suggesting a B cell origin of their disease. No immunoglobulins were detected in the other eight cases; therefore, their cells probably arose from either T cell or null cell origins. Although the presence of both kappa and lambda light chains in Case 19 is not fully understood, there is a possibility of nonspecific staining of immunoglobulins in this case. The results of these...
histological and immunohistological studies suggest that primary CNS lymphoma is indistinguishable from systemic lymphoma except for location.

Postoperative irradiation has been the preferred therapy for primary CNS lymphoma. Sagerman, et al., 26 recommended whole-brain irradiation to a minimum tumor dose of 3500 rads, and Littman and Wang gave whole-brain irradiation with a total of at least 4500 rads at 1000 rads/wk. In our series, mean survival time was 5.5 months in the four patients with subtotal resection only, and 13.5 months in the six patients with subtotal resection and irradiation, demonstrating the effectiveness of whole-brain irradiation. On the other hand, medical treatment including chemotherapy has not been reported as often as has irradiation. Williams, et al., 37 Scully, et al., 29 and Vaquero, et al., 35 reported remission in patients treated with corticosteroids, and proposed a possible mechanism of alteration in the biological activity of tumor tissue or direct cytotoxic effect on the lymphoreticular cells. Methotrexate has also been reported to be effective in the treatment of recurrent CNS lymphomas when given either intravenously 7 or intrathecally. 11 Recently, Neuwelt, et al., 21 reported major tumor regression in three patients following multi-agent chemotherapy given in association with reversible blood-brain barrier opening.

The histological and immunohistological similarity between systemic lymphoma and primary CNS lymphoma suggests that the effective chemotherapeutic agents in the treatment of systemic lymphoma are also effective for primary CNS lymphoma. The agents used are often different in Japan and the United States, and it is postulated that both histological and immunological phenotypes of systemic lymphoma are different in these two countries. The VENP or VEMP combination chemotherapy has been regarded as standard treatment for non-Hodgkin's lymphoma in Japan. In our series, four patients received this combination chemotherapy, along with subtotal resection and irradiation. Their mean survival time was 10.7 months, which is shorter than that of the six patients who received subtotal resection and irradiation. Coltman and McKelvey, et al., 26 reported the superiority of an Adriamycin combination chemotherapy in the treatment of non-Hodgkin's lymphoma. In our series, two patients received CHOP following subtotal resection and survived 1 year 8 months and 2 years 6 months. Another three patients received CHOP combined with subtotal resection and irradiation; two of these survived 1 year 3 months and 3 years 2 months, and the remaining patient is alive and well 12 months after the onset of his symptoms. These results suggest that CHOP is superior to VEMP or VEMP.

ACNU is an antitumor nitrosourea compound synthesized in Japan. It is water-soluble as well as lipid-soluble and has an inhibitory effect on DNA (deoxyribonucleic acid) and protein synthesis. It has been widely used in Japan in the treatment of various types of malignant neoplasm, 22 including systemic lymphoma 19 and malignant brain tumor. 27 Harada, et al., 8 reported its pharmacokinetics in both benign and malignant gliomas following a single intravenous injection, and Yamashita, et al., 28 suggested intra-arterial administration for malignant brain tumors. In our series, the two patients who received ACNU intravenously in conjunction with subtotal resection and irradiation had a survival time of 2 years 5 months and 2 years 4 months. Although only two patients were treated with ACNU, this agent appeared to be effective.

Our immunoglobulin study results did not show a close relationship with the length of survival time. However, with advances in immunohistochemical methods using monoclonal antibodies, T cell subsets 25 and B cell differentiation 2 can be detected in frozen sections of human lymphoid tissue. Recently, Tanaka, et al., 32 reported a new technique using fixed and embedded materials instead of frozen sections. Thus, it is strongly recommended that tumor cells be differentiated further in order to evaluate their susceptibility to irradiation and chemotherapeutic agents. Meanwhile, primary CNS lymphoma should be treated with subtotal resection, whole-brain irradiation, and chemotherapy with CHOP or ACNU initially, and with CHOP or ACNU when the tumor recurs intracranially.

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References

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