Primitive neuroectodermal tumors of childhood

An approach to therapy

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Primitive neuroectodermal tumors are found in the cerebrum of children and young adults. They are clinically highly malignant and have a rapid course from diagnosis to death. Their microscopic pathology reveals 90% to 95% nondifferentiation, frequent mitoses, and small dark cells with no observable cytoplasm. This paper discusses the treatment of three children with this tumor with a combination of surgery, irradiation, and combination chemotherapy. The results of this approach are compared with previous reports in the literature. The average survival in this series is 24 months versus approximately 8 months reported in the literature.

Key Words • brain tumor • primitive neuroectodermal tumor • central nervous system neoplasia • radiation therapy • chemotherapy

In 1973, Hart and Earle described a group of tumors with common pathological and clinical features, which they termed "primitive neuroectodermal tumors." These tumors were found in the cerebrum of children and young adults. They were clinically highly malignant and had a rapid course from diagnosis to death. The gross pathology of these tumors revealed cystic and hemorrhagic features, with sharp borders. Microscopic examination revealed cells that were 90% to 95% nondifferentiated, with variable foci of differentiation along glial and neuronal lines. They were pathologically highly malignant, with small dark cells and no observable cytoplasm. A prominent mesenchymal component was seen.

Recently, there has been increased interest in both the clinical and pathological literature in the entity of primitive neuroectodermal tumors. Using the criteria of diagnosis accepted by Hart and Earle, we reviewed our experience in the treatment of three children with this entity with a combination of surgery, irradiation, and chemotherapy. The results of this approach, when compared with the literature, suggest a limited degree of optimism in the aggressive therapy of these tumors.

Case Reports

Case 1

This 16-year-old white boy presented to the Children's Hospital of Buffalo with bilateral loss of vision and headache of 6 months' duration. On examination, he was an inappropriately cheerful boy. He was noted to have proptosis of the left globe with no bruit or pulsation. Pupils reacted poorly to light. Funduscopic examination revealed long-standing bilateral papilledema. Visual acuity was 20/200 bilaterally. He was found to have left-sided anosmia. The remainder of the neurological examination was normal. X-ray films of the skull showed erosion of bone involving the anterior fossa extending from the left median orbital rim backward to include both sides of the midline, sella, and sphenoid sinus.

The patient was operated on and a partial resection of the tumor mass was accomplished. Follow-up computerized tomography (CT) revealed residual necrotic tumor mass deep in the frontal lobe. The tumor was described grossly as grayish red, vascular, and necrotic, with a cystic cavity. Subsequently, the patient...
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was begun on a radiation program of 5000 rads to the whole brain over a 6-week period, and 1000 rads to the frontal lobe. Combination chemotherapy, including methotrexate, vincristine, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), and dexamethasone, was administered (see Discussion for details).

The patient was stable clinically and x-ray films were unchanged for 11 months, at which time he was noted to have increasing tumor size on CT scan. The only clinical change was increased proptosis. Consequently, the patient was begun on procarbazine. Within 1 month, proptosis had receded. He then remained clinically stable for 6 months, then demonstrated lethargy, confusion, and disorientation. Radioisotope brain scan suggested enlargement of the tumor. Since the patient no longer seemed to respond to chemotherapy, treatment was discontinued. The patient died 1 month later. No autopsy was obtained. The total duration of his survival was 18 months.

Case 2

This 6½-year-old white girl presented with a 6-week history of strabismus, mild headache, and decreased facility of her right arm. Neurological examination revealed a left sixth nerve palsy, bilateral papilledema, and a mild right hemiparesis. Radioisotope brain scan and angiography suggested a large left frontotemporal-parietal mass. Surgery was performed and revealed a cystic tumor involving the temporal lobe with infiltration of the deep white matter. Subtotal removal was accomplished.

The patient was begun on a radiation program of 6000 rads to the brain, and remained asymptomatic for 14 months. She then presented with right-sided weakness, headache, and vomiting, and was found to have a massive increase in tumor size on radioisotope brain scanning. She underwent reoperation and was then treated with methotrexate, administered both intravenously and via an Ommaya reservoir, and with BCNU, vincristine, and dexamethasone for 1 year. The patient responded well and remained asymptomatic for approximately 16 months, when personality change was noted. Studies indicated increasing tumor size. Treatment was reinstituted with BCNU, vincristine, high-dose methotrexate, and procarbazine. The patient's symptoms resolved, and a brain scan showed remarkable improvement. Her symptoms recurred in 6 months, however, and she died 1 month later. Her total survival time from diagnosis was 39 months. The patient died 1 month later. No autopsy was obtained. The total duration of his survival was 18 months.

Case 3

This 10-year-old black girl presented to the Children's Hospital of Buffalo for evaluation of headache, episodes of transient loss of vision, and intermittent vomiting of 3 months' duration. Neurological examination revealed a very mild left hemiparesis and severe papilledema. A CT scan demonstrated a large, partially calcified mass in the right frontal region, with a massive shift of normal structures from right to left (Fig. 1). The mass was subtotally removed. Grossly, the tumor was necrotic and partially calcified. It diffusely invaded the posterior frontal lobe and extended to the falx.

The patient was then treated with radiation and chemotherapy. She received 5000 rads to the whole brain and 1000 rads to the frontal area. She was placed on intravenous and intrathecal methotrexate, BCNU, vincristine, and dexamethasone. Neurological signs and symptoms were minimal, despite the size of the mass on CT and radioisotope brain scanning.

The patient remained neurologically stable, with no increase in tumor size as seen on CT scan for 11 months. At this time, she developed partial and generalized seizures that responded well to anticonvulsant therapy. Thirteen months after diagnosis, lethargy and forgetfulness were noted. She developed pains in her legs, back, and abdomen. A CT scan showed a dramatic increase in the size of the ventricular system, with increased enhancement of the tumor with ad-
Fig. 2. Photomicrograph showing a primitive neuroectodermal tumor with a population of small, nondifferentiated cells with little cytoplasm. H & E, x 240.

administration of contrast material. Recurrent tumor was diagnosed, and chemotherapy was discontinued. The patient deteriorated rapidly and died 16 months after the original diagnosis.

Autopsy revealed tumor in the right frontal lobe, extending into the right caudate nucleus, corpus callosum, and tela choroidea of the third ventricle. Metastases to organs beyond the central nervous system (CNS) included both lungs, trachea, bronchial and pulmonary hilar lymph nodes, pericardium, diaphragm, liver, and spinal cord.

Pathological Features of the Tumors

On examination, these tumors were large, cystic masses located deep within the cerebral hemispheres. They were sharply demarcated from the surrounding brain parenchyma, which seemed to be compressed by the advancing neoplasm. Scattered throughout the tumors, which were generally soft and friable in consistency, were focally hemorrhagic and necrotic areas.

Microscopically, at low magnification, these tumors were highly cellular and, as suggested from the gross impression, well circumscribed from the adjacent brain tissue. Closer inspection revealed small islands of neoplastic cells infiltrating the neighboring parenchyma. The architecture varied from unstructured sheets of cells to cords or nests of cells intersected by trabeculae of mesenchymal tissue composed of abundant collagen and reticulin. The mesenchymal component contained numerous capillaries and larger vessels, often exhibiting striking endothelial proliferation. Zones of endothelial hyperplasia were also randomly distributed within the sheets of neoplastic cells, and at the tumor margins in the brain parenchyma.

Large areas of geographic necrosis were present, as well as small, focal areas of necrosis against which cells tended to be stacked in a manner reminiscent of pseudopalisading. More than 95% of the tumor cells were small, nondifferentiated elements, with little or no discernible cytoplasm. The nuclei were characteristically hyperchromatic and round to oval. Some nuclei were more elongated or irregular in shape. Nucleoli were rarely conspicuous. Occasionally, mitoses were numerous. Groups of cells with a polar orientation resembled spongioblasts. Intercellular fibrillary processes in the vicinity of these cells inconsistently stained like astrocytic fibrils with phosphotungstic acid hematoxylin. There was no evidence of oligodendrocyte differentiation. Perivascular rosettes were identified in one case. Neuroepithelial canals were found in none of these cases. Homer-Wright rosettes, recognized where a ring of tumor nuclei encircled a core composed of a meshwork of fine fibrils, were sometimes seen. Cells with neuronal features, such as abundant cytoplasm, Nissl substance, and prominent nucleoli, were seldom encountered (Fig. 2).

Discussion

Since Hart and Earle first described the pathology of primitive neuroectodermal tumors in 1973, there have been several articles further describing this entity. Admittedly, there has been some nosological confusion in the literature in differentiating these tumors from cerebral neuroblastomas. Nonetheless, 54 cases of primitive neuroectodermal tumors have now been described, in which a consistent pathological and clinical picture has emerged (Table 1). The tumors have occurred in children and young adults, ranging in age from birth to 24 years. The average age of onset was 3.1 years reported by Kosnik, et al., 8.1 years reported by Hart and Earle, 4.6 years reported by Parker, et al., 16 years reported by Marksberry and Challa, and 10.8 years in our children. The tumor is supratentorial, and most frequently lo-
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TABLE 1

Clinical summary of patients with primitive neuroectodermal tumors

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>No. of Cases</th>
<th>Age at Diagnosis</th>
<th>Duration to Diagnosis*</th>
<th>Survival: Diagnosis to Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>Average</td>
<td></td>
</tr>
<tr>
<td>Hart &amp; Earle, 1973</td>
<td>25</td>
<td>birth to 24 yrs</td>
<td>8.1 yrs</td>
<td>10 mos; from onset of symptoms:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 yrs</td>
<td>8.1 yrs</td>
<td>7 mos average</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 mos to 10 yrs</td>
<td></td>
<td>18 mos (16 cases)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mos to 10 yrs</td>
<td>3.1 yrs</td>
<td>7.8 mos average</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mos to 16 yrs</td>
<td>10.8 yrs</td>
<td>within 18 mos, no specific data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parker, et al., 1975</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kosnik, et al., 1978</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Markesbery &amp; Challa,</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duffner, et al., 1981</td>
<td>3</td>
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</table>

* Duration from onset of symptoms to diagnosis.

cated in the frontotemporoparietal region. One primary spinal cord primitive neuroectodermal tumor has been reported. The pathological picture is a highly nondifferentiated malignant tumor with multiple mitoses and primitive cells. Calcification may be seen. The duration of symptoms to diagnosis is generally brief, ranging from 3 weeks to approximately 5 months. Indeed, in one case reported by Hart and Earle, symptoms preceded diagnosis by 3 years, a sufficiently unusual period of time for them to specifically bring it to the reader's attention.

The clinical presentation of these tumors is generally one of increased intracranial pressure and longtract signs. Seizures are occasionally the presenting symptom. Seizures occurred in two of our patients, but only as later complications. The striking clinical finding in our patients was that, despite the huge mass of tumor bulk, the children were relatively asymptomatic. Indeed, they went to school and functioned nearly normally almost until death. The major deficit in our children was inappropriate affect and papilledema, reflecting increased intracranial pressure. Hemiparesis, when present, was mild. Seizures were readily controlled with anticonvulsant medications.

As yet, no one has specifically addressed the question of therapy of these tumors. The treatment approach to these patients was not alluded to by Hart and Earle. Kosnik, et al., referred to the fact that all the children in their series were treated with radiation in a dose of 4000 to 6000 rads. Some of the children received chemotherapy, including methotrexate and later vincristine, BCNU, and prednisone. Doses and possible response to these medications were not discussed in their paper. The review of Parker, et al., did suggest that only two of their seven patients received radiation therapy. One child had received local radiation to the head and died 21 months later with recurrence in the spinal canal. The other patient died with apparent recurrent tumor 18 months after diagnosis, but permission for autopsy was not obtained. Their group was not treated with chemotherapy.

Our children were all treated with surgery, radiation, and the same chemotherapy protocol that we have employed in children with medulloblastoma. As chemotherapy relates to a log-kill hypothesis, the smaller the tumor the more likely is chemotherapy to be effective. Hence, all children are committed to as total a surgical removal as possible. The chemotherapy protocol includes weekly intrathecal methotrexate, 12 mg/sq m; weekly intravenous vincristine, 2 mg/sq m; and dexamethasone, 8 mg/sq m by mouth daily for 5 weeks. The induction phase is given concurrently with radiation therapy, except in cases where there has been previous irradiation. At the conclusion of this phase, the children are begun on high-dose intravenous methotrexate, 500 mg/sq m over 24 hours, plus intrathecal methotrexate, 12 mg/sq m, followed by Leucovorin rescue 24 hours later. Methotrexate is given on three occasions at 3-week intervals. Maintenance begins at the conclusion of this phase and consists of intravenous BCNU, 100 mg/sq m; dexamethasone, 8 mg/sq m by mouth; and vincristine, 2 mg/sq m intravenously each month for the next 2 years.

In Case 1, the patient received surgery, irradiation, and chemotherapy, and was stable from both a clinical and neuroradiological point of view for 11 months. A CT scan then showed evidence of increasing size of the tumor, and clinical examination revealed increasing proptosis. This led us to add procarbazine, 100 mg/sq m by mouth, to the regimen. The proptosis responded readily, and the patient was stable for another 6 months before his death. In Case 2, the
patient responded to initial surgery and radiation therapy for 14 months. At the time of recurrence, she was treated with repeat operation and the chemotherapy protocol as outlined above. She remained symptom-free for 16 months. At this time, neuroradiological and clinical evidence of recurrent tumor prompted us to treat her with procarbazine, 100 mg/sq m by mouth. This produced both clinical and radiological improvement. The patient was then stable for the next 6 months. In Case 3, the patient responded to initial surgery, irradiation, and chemotherapy for a total of 13 months. At this time, she showed signs of diffuse intracranial and extracranial involvement. No further therapy was attempted.

The survival times reported in the literature have been short. Kosnik, et al., reported a survival from time of diagnosis of 7.8 months; Parker, et al., reported 7 months; and all the patients of Markesbery and Challa died within 18 months, although specific durations of survival were not given. Hart and Earle, however, described survival from the onset of symptoms until death. Consequently, this is a difficult group to compare with the rest of the literature. One patient, for example, had a 3-year span from onset of symptoms until diagnosis. If that patient is excluded from their study, they reported a 10-month survival from onset of symptoms until death, with an average duration of symptoms prior to diagnosis of 3 months. Thus, the average survival from diagnosis reported in the literature is approximately 8 months. Our patients, as treated above, had survival times of 16, 18, and 39 months, with an average survival period of 24 months. These numbers are much too small to make any statement about the differences in overall survival time, but the clinical responses of the patients suggest that the tumor may be responsive for varying periods of time to aggressive radiation and chemotherapy. It should be noted, however, that treatment either stabilized these patients’ symptoms or provided clinical improvement. Only in Case 2 was there a clearly defined improvement on radiological studies following therapy.

An important consideration in the approach to primitive neuroectodermal tumors is the question of extracranial metastases. Parker reported one case of metastases to the spinal cord. One of our patients also had metastases to the spinal cord but, in addition, had widespread extra-CNS metastases to the lungs, the tracheal, bronchial and pulmonary hilar lymph nodes, the pericardium, the diaphragm, and the liver. Thus, the approach to these tumors should include at least radiation to the entire craniocaudal axis. In view of our one case with extensive extracranial metastases, consideration of the role of systemic chemotherapy in this tumor is extremely important.

Although none of the children in this study developed significant toxicity from the chemotherapy regimen, a report on treatment would not be complete unless the more common potential side-effects were mentioned. The administration of BCNU has been associated with delayed bone marrow depression, and, therefore, BCNU was not given concurrently with radiotherapy. Pulmonary toxicity with BCNU has been reported with increased frequency. Vincristine is associated with peripheral neuropathy, myopathy, jaw pain, and obstipation. Methotrexate has been associated with mucositis, leukoencephalopathy, seizures, and paraplegia. The delivery of methotrexate via an Ommaya reservoir in children with brain tumors has been associated with necrotizing leukoencephalopathy. The combined administration of methotrexate and radiotherapy in children with altered cerebrospinal fluid resorption must be used with caution.

Thus, children on this and other chemotherapy protocols need close monitoring. At our institution, bi-monthly blood counts, liver function tests, and general physical examinations are carried out. Neurological examinations are performed monthly by child neurologists, and CT scans are obtained every 6 months or more frequently as needed. Prior to institution of radiotherapy or chemotherapy, intelligence quotient evaluations and baseline endocrine studies are done.

As the entity of primitive neuroectodermal tumors becomes more widely accepted, a better appreciation of the natural history and response to therapy will be obtained. At the present time, however, there is a suggestion that these tumors will respond to intensive radiation and chemotherapy. Their pathological resemblance to medulloblastomas makes this response not surprising. Treatment of medulloblastomas with radiation is now well accepted and produces 5-year survival rates of 40% to 50%. Most recently, aggressive therapy with chemotherapy in both recurrent and de novo medulloblastomas is becoming more widely accepted. Rapid rate of growth, high mitotic index, and radiosensitivity are characteristics that influence response to chemotherapy. Thus, the more highly malignant tumors may be more susceptible to chemotherapy. Primitive neuroectodermal tumors fulfill these criteria and, therefore, may be expected to respond to chemotherapy.

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