Low-grade astrocytoma with neuraxis dissemination at diagnosis

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Little is known about low-grade astrocytoma with neuraxis dissemination at diagnosis. A review of medical records identified this phenomenon in eight of 150 pediatric patients evaluated between 1985 and 1994 for histologically confirmed low-grade astrocytoma. These patients (five male and three female) ranged in age from 5 months to 20 years (median 8 years). Symptoms of neuraxis disease were minimal or absent. Primary tumor sites were the hypothalamus in four cases, brainstem/spinal cord in three, and temporal lobe in one. Patterns of dissemination (evaluated by computerized tomography and/or magnetic resonance imaging techniques) appeared to be related to the primary site: hypothalamic tumors metastasized along the ventricular cerebrospinal fluid pathways, and tumors in other locations disseminated along subarachnoid pathways. Following initial treatment with chemotherapy (in three), partial resection (in one), radiation therapy (in three), and chemotherapy plus irradiation (in one), four patients required salvage therapy for progressive or recurrent disease. Seven of the eight patients are alive with stable or progressive disease 6 to 105 months postdiagnosis (median 15 months). Low-grade astrocytoma with initial neuraxis dissemination is responsive to chemotherapy and radiation, a proportion showing periods of stable disease. The optimum therapy or combination of therapies remains unclear.

KEY WORDS • low-grade astrocytoma • neuraxis • dissemination

DISSEMINATION of tumor cells along the cerebrospinal fluid (CSF) pathway has been reported in virtually all types of primary central nervous system (CNS) neoplasms. This phenomenon has been observed both at presentation and at the time of disease progression, primarily in medulloblastomas, germ-cell tumors, or high-grade gliomas. Neuraxis dissemination at diagnosis in low-grade gliomas has been reported only anecdotally, and little is known about the precise patterns of dissemination, clinical presentation, and treatment responsiveness of this subset of CNS tumors. We therefore reviewed the records of all newly diagnosed patients with biopsy-proven low-grade astrocytomas referred to a pediatric cancer research center to determine the frequency and characteristics of neuraxis dissemination in otherwise “benign” tumor presentations.

Clinical Material and Methods

Between 1985 and 1994, 150 patients with biopsy-proven low-grade astrocytomas were evaluated by the Brain Tumor Team at St. Jude Children’s Research Hospital/LeBonheur Children’s Medical Center. All patients underwent neuroimaging studies of the primary site that included computerized tomography (CT) and/or magnetic resonance (MR) imaging. We identified and reviewed the records of patients with neuroimaging or surgical evidence of neuraxis dissemination at diagnosis. The extent of dissemination was documented by CT myelography or spinal MR imaging with gadolinium enhancement in patients with intracranial disease and by head CT and MR imaging in those with spinal cord primaries. The CSF cytology was examined in patients with...
neuraxis dissemination unless there was evidence of ventricular or subarachnoid obstruction. Gross total resection of the primary lesion was attempted when tumor size and location permitted this approach; in other cases surgery was limited to biopsy and/or partial resection. No attempt was made to obtain biopsy material from sites of metastatic disease. In all cases, tumor histology was reviewed by one of the authors (J.J.J.) to confirm the original diagnosis of low-grade neoplasms and the specific tumor type (defined as astrocytoma or juvenile pilocytic astrocytoma).7

Following biopsy or resection, patients with disseminated disease were treated with chemotherapy and/or radiation therapy. Chemotherapy consisted of cisplatin or carboplatin, alone or in combination with vincristine or etoposide. Craniospinal irradiation to total doses ranging from 35.2 to 38.2 Gy (conventional fractionation) and from 40.0 to 48.4 Gy (hyperfractionation) was given, with a boost to the primary tumor.

Neuroimaging studies were repeated at regular intervals. For patients with measurable primary tumors after surgery, treatment response was determined by calculating changes in the cross-sectional diameter of the primary tumor. Response to radiation therapy was evaluated 8 weeks after treatment was completed; chemotherapy responses were evaluated at regular intervals during treatment and at the termination of chemotherapy.

Responses at the primary site were categorized as follows: complete response, resolution of all tumor on MR images or CT scans; partial response, a 50% or greater decrease in the tumor size; stable disease, less than 50% decrease or less than 25% increase in tumor size; and progressive disease, a 25% or greater increase in primary tumor size. Measurable metastases were categorized similarly. For disseminated disease present only as a thin coating of the underlying brain or spinal cord, disease response was described as “improved,” “no change,” or “progressive disease” with no attempt at quantitation.

Results

Of 150 patients with a confirmed diagnosis of low-grade neoplasms and the specific tumor type, 86 were classified as low-grade astrocytoma and 64 as juvenile pilocytic astrocytoma. The majority of patients had disseminated disease (79%), with fewer cases presenting with isolated disease (21%).

TABLE 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age† (yrs), Sex</th>
<th>Presenting Clinical Features</th>
<th>Primary Site &amp; Extent of Surgery</th>
<th>Imaging Modality</th>
<th>Primary Neuraxis</th>
<th>Pathology</th>
<th>Primary Therapy</th>
<th>Primary Tumor</th>
<th>Metastatic Site</th>
<th>Response to Primary Therapy</th>
<th>Survival Time‡ (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5/12, M</td>
<td>no visual fixation</td>
<td>hypothalamus, biopsy</td>
<td>spinal cord, ventricle, cerebellum</td>
<td>MRI</td>
<td>MRI</td>
<td>astrocytoma</td>
<td>CBCDA</td>
<td>SD</td>
<td>NC</td>
<td>21 +</td>
</tr>
<tr>
<td>2</td>
<td>3, M</td>
<td>diminished spinal flexion</td>
<td>hypothalamus, biopsy</td>
<td>cerebral hemisphere, spinal cord, ventricle, cerebellum</td>
<td>MRI</td>
<td>MRI</td>
<td>JPA</td>
<td>CBCDA/VCR</td>
<td>SD</td>
<td>NC</td>
<td>13 +</td>
</tr>
<tr>
<td>3</td>
<td>5, M</td>
<td>seizure, rotatory nystagmus</td>
<td>hypothalamus, biopsy</td>
<td>spinal cord, ventricle, cerebellum</td>
<td>MRI</td>
<td>MRI</td>
<td>astrocytoma</td>
<td>CBCDA/VCR</td>
<td>PD</td>
<td>PD</td>
<td>6 +</td>
</tr>
<tr>
<td>4</td>
<td>16, M</td>
<td>headache</td>
<td>hypothalamus, biopsy</td>
<td>spinal cord, ventricle, cerebellum</td>
<td>MRI</td>
<td>MRI</td>
<td>JPA</td>
<td>XRT</td>
<td>PD</td>
<td>PD</td>
<td>14 +</td>
</tr>
<tr>
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<td>seizure</td>
<td>thoracic cord, biopsy</td>
<td>cerebral hemisphere, cerebellum</td>
<td>CT</td>
<td>CT</td>
<td>astrocytoma</td>
<td>CDDP/VP-16+XRT</td>
<td>SD</td>
<td>SD</td>
<td>91 +</td>
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<td>13, M</td>
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<td>MRI</td>
<td>MRI</td>
<td>astrocytoma</td>
<td>XRT</td>
<td>SD</td>
<td>PD</td>
<td>15 +</td>
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<tr>
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<td>pons, biopsy</td>
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<td>MRI</td>
<td>astrocytoma</td>
<td>XRT</td>
<td>SD</td>
<td>PD</td>
<td>10</td>
</tr>
<tr>
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<td>headache, hemiparesis</td>
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<td>cerebral hemisphere</td>
<td>CT</td>
<td>CT</td>
<td>myelogram</td>
<td>JPA surgery</td>
<td>PD</td>
<td>NC</td>
<td>105 +</td>
</tr>
</tbody>
</table>

* MRI = magnetic resonance imaging; CT = computerized tomography; JPA = juvenile pilocytic astrocytoma; CBCDA = carboplatin; VCR = vincristine; XRT = radiation therapy; CDDP = cisplatin; VP-16 = etoposide; SD = stable disease; PD = progressive disease; NC = no change.
† Age at presentation.
‡ Time of survival after diagnosis; + = surviving patient.
grade astrocytoma, eight (5.3%) had neuroimaging evidence of neuraxis dissemination at initial diagnosis. These five male and three female patients ranged in age from 5 months to 20 years (median age 8 years). The primary tumor was located in the hypothalamus in four cases, the temporal lobe in one, the spinal cord in two, and the pons in one. Five tumors were classified as astrocytoma, and three as juvenile pilocytic astrocytoma. The imaging modalities used to define the extent of disease are outlined in Table 1, along with the patients’ clinical characteristics and treatment histories.

All four patients with hypothalamic tumors were found to have tumor deposits lining the walls of the ventricles and in the subarachnoid space overlying the cerebellum and spinal cord; one child also had metastatic disease overlying the cerebral hemispheres. Figures 1 and 2 present contrast-enhanced MR images demonstrating disease dissemination intracranially and over the spinal cord. Figure 1 shows diffuse CSF enhancement following gadolinium contrast infusion; this is best revealed by the subtraction technique (Fig. 3) and is a sign of leptomeningeal disease.\(^5\)\(^,\)\(^18\) Despite the extensive spinal subarachnoid metastases shown by imaging studies in each of these four cases, only one child (Case 2, Table 1) had symptoms of leptomeningeal disease, with diminished spinal flexion. The CSF cytology was negative in the two patients for whom these studies were available. Following biopsy of the primary tumors, three of these patients were treated with platinum-based chemotherapy. One patient is alive with stable disease 3 months after the completion of scheduled chemotherapy. The second patient continues on chemotherapy with stable disease, whereas the third patient had progressive disease at the primary and metastatic sites 2 months after beginning chemotherapy. He was subsequently treated with radiation therapy and is alive with stable disease 4 months postirradiation. The fourth patient was initially treated with craniospinal radiation alone and had markedly progressive symptomatic disease at his 8-week evaluation. He is currently being followed with progressive disease after showing a transient response to Topotecan in a phase I trial.

The two patients with spinal cord tumors and one with a focal pontine tumor also had extensive leptomeningeal metastases coating the spine, cerebellum, cerebral convexities, and basal cisterns in various combinations. Figure 4 shows a contrast-enhanced CT scan displaying leptomeningeal metastases in the interpeduncular fossa, ambient cistern, and sylvian fissure in a patient with a spinal cord tumor. Only one of these three patients had positive CSF cytology. Unlike the patients with hypothalamic tumors, these children had no intraventricular disease. One of these patients was treated with a 4-month
neuraxis dissemination was easily identified on the initial diagnostic imaging studies in seven of our cases. In the eighth, although metastasis was not diagnosed prior to surgery, retrospective review of the initial CT scan from the referring institution revealed a metastatic tumor deposit. Although the small number of patients precludes strong comparisons of imaging modalities, MR imaging with gadolinium enhancement appears to be sensitive in detecting neuraxis dissemination.² Of note is the fact that neuraxis dissemination was detectable on images obtained

Discussion

Neuraxis dissemination of low-grade astrocytomas is an uncommon occurrence. Using modern imaging techniques, we identified neuraxis dissemination at the time of diagnosis in 5% of a large series of consecutively accrued patients with low-grade astrocytoma. In contrast to the present series, most reports have described neuraxis dissemination concurrent with or following recurrence at the primary site. Investigators at the Children’s Hospital of Philadelphia found neuraxis dissemination in 6 (3.7%) of 162 patients with low-grade astrocytoma, only one of whom was newly diagnosed.² Another group reported disseminated disease in 18% of children and adults with hypothalamic juvenile pilocytic astrocytomas at the time of disease progression, but none had apparent dissemination at diagnosis.¹¹

Autopsy studies suggest that dissemination of tumor cells via the CSF pathways is probably the primary mechanism of metastases within the CNS.²⁰ Spread via the ventricular CSF was the most likely mechanism of tumor dissemination in our four patients with hypothalamic primary sites. These tumors arise as discrete neoplasms in the floor of the third ventricle, impinging on the optic and infundibular recesses. As they grow, they may breach the ependymal epithelium and shed tumor cells into the third ventricular cavity; normal CSF flow would then carry tumor cells through the aqueduct of Sylvius, the fourth ventricle, and eventually through the foramina of Magendie and Luschka to the rest of the intracranial and spinal subarachnoid space. Viable tumor cells that penetrate the ependymal lining of the ventricle can become attached to the ependyma or leptomeninges at distant sites, proliferating to form metastatic masses. Obstructive hydrocephalus is thought to favor ependymal implantation.²⁰ In the absence of hydrocephalus, tumor cells do not appear to attach easily to ciliated ependymal surfaces and subarachnoid metastases may be more likely.

A different pattern of spread was seen in the three patients with tumors of the brainstem or spinal cord, whose disease disseminated only to the spinal and cerebr al subarachnoid spaces. This pattern suggests direct shedding of tumor into the subarachnoid space and transport via CSF to distant sites within the neuraxis. The absence of ventricular metastases in these cases suggests the inability of tumor cells to move and implant against the direction of normal CSF flow.

The one hemispheric tumor had a pattern of disease spread similar to that described in high-grade gliomas. The presumed mechanism involves disaggregation of individual tumor cells and their passive spread through the interstitial space with entry into the perivascular (Virchow–Robin) space. The perivascular sheath has been shown to be an extension of the pia and to contain fenestrations at the arteriolar level. These fenestrations may offer parenchymal tumor cells direct access to the perivascular and subarachnoid spaces.¹⁹,²⁵

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![Fig. 4. Case 5. Contrast-enhanced computerized tomography showing nodular leptomeningeal metastases from a spinal cord tumor in the interpeduncular fossa and the ambient cistern. There are also nodular metastases in the sylvian fissures bilaterally.](image-url)
Low-grade astrocytoma with neuraxis dissemination

to define the primary tumor location. Thus, especially in view of the low incidence of neuraxis dissemination, more extensive neuroimaging does not appear justified in the evaluation of patients with low-grade astrocytoma when imaging of the primary tumor does not show evidence of neuraxis dissemination.

Given the extensiveness of neuraxis dissemination in all but one of our cases, neurological symptoms were remarkably limited. In contrast, patients with histologically malignant tumors have pronounced symptoms even with tumor burdens less than noted in the current series.22

The paucity of clinical findings in our low-grade astrocytoma patients with neuraxis dissemination may represent a diminished capacity for arachnoid invasion.

Long-term disease stabilization has followed radiation therapy in two of our cases and chemotherapy in one. The response to chemotherapy as salvage for progressive disease postirradiation has been of short duration. In general, experience with radiation therapy as salvage for young patients whose disease progresses on initial chemotherapy remains limited. Thus, the optimum treatment for these patients is yet to be determined. Our treatment approach in younger children is in accord with general trends in contemporary pediatric neurooncology in that we attempt to delay radiation therapy by the initial use of chemotherapy.3 Treatment with carboplatin, alone or combined with vincristine, has been reported to achieve durable disease stabilization in patients with primary or recurrent low-grade gliomas; such an approach appears warranted in a setting marked by often asymptomatic, widespread neuraxis disease in young children.4,13,15

In summary, we have found neuraxis dissemination at diagnosis in 5% of children with low-grade astrocytoma. Disseminated disease is typically discernible on imaging directed to the primary tumor site. The course of disease varies from rapid progression despite chemotherapy and radiation therapy to prolonged stabilization.

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References


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