Leptomeningeal dissemination at diagnosis of pediatric low-grade neuroepithelial tumors

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The goal of this study was to describe the demographic, histologic, and prognostic features of children with low-grade neuroepithelial tumors (LGN) of the CNS presenting with leptomeningeal metastases (LM) at diagnosis. We identified 528 newly diagnosed LGN children, 13 (3%) of whom had LM at diagnosis. LM was defined by neuroimaging, clinical evidence, and/or biopsy. The charts were reviewed and patients contacted to validate the demographic data, treatment, and clinical status. The distribution of LM patients by primary tumor site was diencephalon, 5; cerebrum, 2; spinal cord, 3; brainstem, 2; and cerebellum, 1. Six of 8 patients with LM had durable objective responses to chemotherapy. The 5-year progression-free survival of patients with LM at diagnosis was 17%, compared to 85% (95% CI, 80%–91%) for those with localized LGN who had a gross total resection and 51% (95% CI, 44%–52%) for those with localized LGN who had less aggressive surgery (P < 0.0001). Only 1 of these 13 LM patients died. The 5-year overall survival of the localized LGN group with a gross total resection was 97% (95% CI, 92%–99.9%), and that of the localized LGN group with less aggressive surgery was 88% (95% CI, 84%–95%) (P = 0.004). The 3% frequency of LM at diagnosis is likely an underestimate since patients with newly diagnosed LGN were not routinely staged. We suggest that staging be considered in the following circumstances: diencephalic primary site, unexplained hydrocephalus, clinical features suggestive of LM, and before adjuvant therapy is initiated. The prognosis for children with LM at diagnosis is favorable, and its identification alters therapeutic strategies.

Low-grade neuroepithelial tumors (LGNs) are the most common primary CNS tumor in children, representing 50% to 60% of cases. They typically occur in the cerebellum, cerebrum, optic chiasm, and hypothalamic region and less frequently in the brainstem and spinal cord. LGNs typically manifest a low mitotic rate (<1.5%) and exhibit a favorable prognosis. For patients whose tumors are amenable to a gross total surgical resection, the 10-year survival is greater than 90% (Campbell and Pollack, 1996; Pollack et al., 1995). When a gross total resection (GTR) cannot be accomplished at least initially, there is a less favorable 10-year survival, varying from 50% to 86% (Campbell and Pollack, 1996; Scott and Mickle, 1987; Woo et al., 1988). Approximately 5% of LGNs behave aggressively, as manifested by a higher rate of localized recurrence or a tendency to metastasize. The reported incidence of leptomeningeal metastases (LM) in low-grade glioma (LGG) or low-grade astrocytoma at recurrence varies from 3% to 10% (Civitello et al., 1988; Mamelak et al., 1994; Pollack et al., 1994), a phenomenon recognized primarily after the start of the MRI era, but the incidence of LM in LGN at diagnosis is unknown. Although metastatic spread from a primary malignant CNS tumor, such as primitive

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neuroectodermal tumor and glioblastoma, implies more aggressive behavior and a worse prognosis, the significance of this in LGN is not clear.

We have identified 24 patients out of 528 LGN cases in our computerized database with LM, 13 of whom had LM at diagnosis. The purpose of this study was to identify any unique clinical or histologic features of this small cohort of patients with LM at diagnosis.

Methods

A total of 528 patients with LGN were identified from our database of pediatric primary CNS tumors diagnosed between 1983 and 1997. In 1986, we began entering data on all patients diagnosed at our institution from 1983 to date, and the database was maintained consistently from this time. The data of all LGG patients diagnosed between 1983 and 1997 were retrospectively reviewed for this study. The cutoff point for follow-up of data was 1999. The database was started at New York University Medical Center and continued following our move to Beth Israel Medical Center in 1996. Both institutions are tertiary care facilities. Inclusion criteria were as follows: age less than 21 years and tissue confirmation of LGN, including astrocytoma and mixed glial and neuronal tumors. Ependymomas and diffuse pontine gliomas were excluded. The term diencephalon was allocated to all tumors arising from the hypothalamus, optic chiasm, or thalamic region, as it is sometimes difficult to determine the specific site of origin of the tumor. LM was defined by several criteria: neuroimaging, clinical neurological corroboration when available, and cerebrospinal fluid cytology or biopsy confirmation of metastases. MRI evidence of leptomeningeal disease was accepted only if the MRI was done prior to surgery or at least 2 weeks after surgery to avoid false positive leptomeningeal enhancement. A subset of 13 patients was identified with LM at diagnosis. Those patients who did not have LM at diagnosis served as the control group. Since staging was not part of the standard evaluation of LGN in our institution, the retrospective method of ascertainment was likely to underestimate the true incidence of LM. Charts were reviewed to determine tumor location, histology, treatment, and outcome. The neuropathology was re-reviewed by one of the authors for all 13 LM cases. Follow-up was obtained in the clinic or by telephone survey. Statistical analysis of progression-free survival and overall survival was performed with the Kaplan-Meier procedure and log-rank tests to test the hypothesis of no difference between groups.

Results

Only 3% (13/528) of LGN patients had LM at diagnosis. Eleven of the 515 patients who had localized disease at diagnosis were in the previously described group of LM patients at the time of progression (Hukin et al., 2002). Evidence of LM in this cohort of 13 patients was noted on gadolinium-enhanced MRI in all cases, 1 at follow-up only, as the original diagnosis was by myelogram, CT, and biopsy. Those with symptomatic LM are outlined in Table 1. Tissue confirmation of LM was made in 8 cases, and the histology was the same as that for the original primary tumor site. We were unable to identify any tumor cells in any of the 4 patients in whom the cerebrospinal fluid was examined. The male-to-female ratio in the patient cohort with localized disease was equal to that in the LM patient cohort. The median age at diagnosis was similar in the 2 groups, 6.7 years (0–20.9 years) in those with localized disease and 8.7 years (0.25–17 years) in those with LM at diagnosis. The primary tumor site, histology, metastatic site, and age at diagnosis for the 13 patients with LM from an LGN are outlined in Table 1.

Table 1. Clinical characteristics of the 13 patients with LM at diagnosis

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Histology</th>
<th>Tumor primary location</th>
<th>Sites of Initial Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PA</td>
<td>Diencephalon</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>LGA</td>
<td>Diencephalon</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>4.1</td>
<td>Brainstem</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>Spinal cord</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>6.3</td>
<td>Diencephalon</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>8.7</td>
<td>Spinal cord</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>8.7</td>
<td>DNT</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>10.2</td>
<td>Brainstem</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>10.2</td>
<td>Cerebellum</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>10.3</td>
<td>Cerebral</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>10.4</td>
<td>PA</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>11.4</td>
<td>Mixed glioma</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>17</td>
<td>PA</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: DNT, dysembryoplastic neuroepithelial tumor; LGA, low-grade astrocytoma; PA, pilocytic astrocytoma.
Histology

Among the 528 children with newly diagnosed LGN, there was the expected distribution of histologic subsets, with pilocytic astrocytoma (PA) (24%, 126/528), fibrillary astrocytoma (38%, 205/528), and ganglioglioma (22%, 115/528) being more commonly represented. Less common subsets included mixed gliomas (6%, 31/528) and dysembryoplastic neuroepithelial tumors (6%, 31/528). There were 20 additional localized LGGs of other histology, including oligodendroglioma, subependymal giant cell astrocytoma, ganglioneurocytoma, ganglioneurofibroma, glioneurocytoma, glioneurofibroma, and glioma not otherwise specified, with few numbers in each category, none of which had evidence of LM at diagnosis. Evidence of LM at diagnosis was seen in 4% (5/126) of the PAs, 2% (2/115) of the gangliogliomas, 2% (4/205) of the low-grade fibrillary astrocytomas (LGAs), 3% (1/31) of the mixed gliomas, and 3% (1/31) of the dysembryoplastic neuroepithelial tumors.

Tumor Location

Among the 528 children with newly diagnosed LGN, the most common primary tumor location was in the posterior fossa (203 patients). Other sites included cerebral cortex (24%, 127/528), diencephalon (19%, 100/528), and spinal cord (19%, 98/528). The relatively high representation of primary spinal cord tumors in this series likely is a reflection of the pattern of referrals to our institution. Nine of the diencephalic tumors occurred in patients with neurofibromatosis type 1, and none of these had LM. The diencephalon was the most common primary tumor site for patients with LM, representing 39% (5/13) of the cases. Thus, evidence of LM was found at diagnosis in 5% (5/100) of diencephalic tumors, 3% (3/98) of spinal cord tumors, 2% (2/127) of cerebral cortex tumors, and 2% (3/203) of posterior fossa tumors. Statistical analysis using chi-square does not show any significant difference in LM between any of these groups. It is not within the scope of this report to state whether the lack of statistical association found is because of lack of power of the sample or because there is truly no biological relationship.

Treatment

Table 2 shows the details of management of each of the LM patients. A comparison of therapy for the 13 patients with LM at diagnosis and the 515 patients without LM at diagnosis is outlined below. Surgical procedures at diagnosis in the LM patients included a shunt (46%,
6/13), biopsy (54%, 7/13), and GTR (0%, 0/13), as did those for the 515 patients with localized disease (shunt, 22%; biopsy, 5%; GTR, 43%). In the LM group, 70% (9/13) of the patients received adjunctive therapy: 8 patients received chemotherapy and 4 received involved-field boost, with additional craniospinal radiation in 3; the 4 remaining patients had radical resections of symptomatic metastatic lesions only, as these patients did not want to pursue either radiation therapy or chemotherapy. In contrast, in the group of patients with localized disease, only 23% (118/515) received adjunctive therapy: 66 patients received chemotherapy and 75 patients received involved-field radiotherapy, 2 of these 75 patients receiving additional craniospinal radiation. Figure 1 demonstrates the resolution of leptomeningeal disease following chemotherapy.

**Morbidity**

All patients with LM at diagnosis had at least short-term improvement with relief of symptoms following treatment. Surgical intervention provided symptomatic improvement in 9 of 13 patients; radiation therapy improved function in the short term in 4 patients, although long-term cognitive dysfunction developed in 2; chemotherapy provided symptomatic relief as well as a radiological response in 6 of 8 patients. Table 3 demonstrates the status of patients with LM at the time of last follow-up.

**Survival**

By observation, the 5-year progression-free survival was 17% for those with LM, compared to 85% (95% CI, 80%–91%) for those with localized LGN who had a GTR and 51% (95% CI, 44%–52%) for those with localized LGN who had less aggressive surgery (NGTR) \( P < 0.0001 \) (Fig. 2). These results were significantly different even after adjusting for multiple comparisons. For example, when the LM group is compared with the NGTR group, the \( P \) value is 0.0007. Only 1 of 13 LM patients died.

The 5-year overall survival of the patients with localized disease was 97% (95% CI, 92%–99.9%) for those who had a GTR, compared to 88% (95% CI, 84%–95%) for those who had an NGTR \( (P = 0.004) \) (Fig. 3). All \( P \) values are for overall survival (i.e., time to the last event, either survival or tumor progression) between groups, but 5-year proportions and confidence intervals are presented by observation of the Kaplan-Meier analysis, as 5-year survivals are what is conventionally described in the oncology literature. Confidence intervals are presented for data at the fifth year, or as close to it as an event in either group presented.

**Discussion**

LM in children with LGN is rare but probably underdiagnosed. Only 3% of children with LGN in our series

<table>
<thead>
<tr>
<th>Patient Code</th>
<th>Neurological status at follow-up</th>
<th>Endocrine Status</th>
<th>Cognition</th>
<th>Disability status</th>
<th>Disease status since last intervention</th>
<th>Radiology status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dead</td>
<td>Dead</td>
<td>Dead</td>
<td>Dead</td>
<td>Died of disease progression</td>
<td>LM, primary</td>
</tr>
<tr>
<td>2</td>
<td>Hemianopia, ataxia, hemiparesis, dysphasia</td>
<td>Panhypopituitarism</td>
<td>Borderline mental retardation prior to radiation</td>
<td>Walker, g-tube</td>
<td>Stable</td>
<td>LM, primary</td>
</tr>
<tr>
<td>3</td>
<td>Hemiparesis</td>
<td>Normal</td>
<td>Mild impairment</td>
<td>Independent</td>
<td>Improved</td>
<td>Small primary residual</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Independent</td>
<td>Improved</td>
<td>LM, primary</td>
</tr>
<tr>
<td>5</td>
<td>Visual acuity, 20/70 right</td>
<td>Normal</td>
<td>Grade 3 education, immature</td>
<td>Independent</td>
<td>Progression</td>
<td>LM, growth of primary with hemorrhage</td>
</tr>
<tr>
<td>6</td>
<td>Paraplegia</td>
<td>Normal</td>
<td>Normal</td>
<td>Wheelchair</td>
<td>Improved</td>
<td>LM</td>
</tr>
<tr>
<td>7</td>
<td>Paraparesis, urgency</td>
<td>Normal</td>
<td>Normal</td>
<td>Walker</td>
<td>Progression</td>
<td>LM, large primary</td>
</tr>
<tr>
<td>8</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Independent</td>
<td>Improved</td>
<td>Small primary residual</td>
</tr>
<tr>
<td>9</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Independent</td>
<td>Improved</td>
<td>LM, primary</td>
</tr>
<tr>
<td>10</td>
<td>Paraparesis</td>
<td>Amenorrhoea</td>
<td>Normal</td>
<td>Wheelchair (drives car)</td>
<td>Remission</td>
<td>No tumor</td>
</tr>
<tr>
<td>11</td>
<td>Mild quadraparesis</td>
<td>Normal</td>
<td>Mild impairment</td>
<td>Poor hand dexterity; school aide; running</td>
<td>Improved</td>
<td>LM, small primary</td>
</tr>
<tr>
<td>12</td>
<td>Mild neuropathy</td>
<td>Normal</td>
<td>Learning disability</td>
<td>Independent</td>
<td>Improved</td>
<td>LM, primary</td>
</tr>
<tr>
<td>13</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Independent</td>
<td>Improved</td>
<td>LM, spontaneous decrease in one</td>
</tr>
</tbody>
</table>

Abbreviation: LM, leptomeningeal metastases.
Fig. 1. MRI T1 images. A. Spin echo image with gadolinium: Primary tumor in right cerebellar peduncle. B. Spin echo image with gadolinium: Leptomeningeal enhancement in cisterns. C. Gradient echo image with gadolinium: Primary tumor in right cerebellar peduncle partial response to chemotherapy with carboplatin and vincristine. D. Gradient echo image with gadolinium: Resolution of leptomeningeal disease following chemotherapy with carboplatin and vincristine.
had LM at diagnosis. All 13 children had neuroimaging documentation, which was confirmed histologically in 8. Only 5 patients had symptomatic leptomeningeal disease. Twelve had either the clinical suggestion of metastases or metastases noted on the initial MRI, leading to staging, which confirmed the clinical suspicion and delineated the extent of disease. The true incidence will remain unknown unless staging is performed routinely on all LGNs. In this study, there is a trend for dissemination to occur more commonly in patients with diencephalic and astrocytomas PAs, but the numbers are too small to be statistically significant. Identification of LM may lead to a more conservative surgical approach in addition to altering the timing, modality, and extent of adjuvant therapy. Although we have no evidence of whether LM alters the favorable prognosis of LGN in terms of survival, it does appear to be associated with earlier progression.

Diagnostic dilemmas in this disease are outlined below. None of the 13 patients with LM in this series were identified with positive CSF cytology, although only a small number were sampled. Either the low number of tumor cells in the CSF, the volume, or the inability of the pathologist to characterize them as distinct from normal glial cells may account for that. Only a few cases of LM in LGNs reported in the literature were confirmed with positive CSF cytology (Cinalli et al., 1995; Civitello et al., 1988; Doireau et al., 1999; Gajjar et al., 1995; Mamelak et al., 1994; McCowage et al., 1996; Perilongo et al., 1997; Pollack et al., 1994; Shapiro and Shulman, 1976). Our study not only considerably increases the total experience reported to date but also provides a crude estimate of incidence in a wider spectrum of low-grade lesions, low-grade neuroepithelial tumors. The median age among the published cases is 5 years (0.5–20 years) compared to our study of 8.7 years (0.25–17 years). Although the literature suggests a male predominance of 2:1, our study did not show any sex predilection. Of the 20 published cases to date, 52% were PAs, and the most common primary site was the hypothalamus (62%). Among our group, 69% were either LGAs or PAs, and 39% arose from the diencephalon.

The treatment and outcome of these 20 published cases is as follows. Four patients died, at 18, 25, and 60 months postdiagnosis. (The patient who died at 25 months did not receive adjuvant therapy.) Radiation induced a complete response in 1 patient (overall survival 48+ months) and stabilization of disease in 3 patients (overall survival 6+, 105+, and 156+ months). Chemotherapy induced tumor regression in 4 patients (overall survival 6+, 23+, 48+, and 60+ months), a transient response in 2 patients (overall survival 14+ and 15+ months).
months), and stable disease in 3 patients (overall survival 21+, 13+, and 17+ months). One patient had stable disease following a combination of radiation and chemotherapy (survival 91+ months). For 2 patients, the treatment and length of survival is unclear from the report. Of the 20 published cases, 2 of 4 patients with primary hypothalamic disease that presented prior to 1 year of age died, in spite of adjuvant therapy, 18 and 60 months following diagnosis. This latter observation is in keeping with our observation that hypothalamic tumors diagnosed with dissemination when the patient is less than 1 year of age may be unfavorable prognostic factors.

Our series suggests that treatment of symptomatic lesions may reduce disease-related morbidity. Craniospinal radiation appears to be effective in stabilizing disseminated disease and inducing regression of disease (patients 2, 3, and 10), although it may not be curative. This is consistent with historic data of involved-field radiation for LGG at progression (Bauman et al., 1999; Pollack et al., 1995). Of LM patients who received chemotherapy either at diagnosis or progression, 75% (6/8) had some form of response, although this was only transient in 2 patients. The other 25% (2/8) of the patients progressed at the primary site through the first trial of chemotherapy. The response rate in our series is better than the previously published data for LGG—an objective response rate of 56% following carboplatin and vincristine therapy (Packer et al., 1997) and 36% following nitrosourea-based therapy (Prados et al., 1997). Of the patients with LGGs reported by Packer et al. (1997), 4% had disseminated disease, and Prados et al. (1997) do not report any patients with LM. Spontaneous regression of untreated lesions can occur (patient 13), which is in keeping with the historic experience of LGGs in general (Giannini and Scheithauer, 1997). This disease tends to behave in a more indolent fashion than other primary CNS tumors with evidence of dissemination. Our series suggests that adjuvant therapeutic intervention may decrease morbidity and tumor bulk at least in the short term.

The long-term morbidity of the disease (as well as length of treatment) was greater in those with LM than in historic controls with localized LGN (Campbell and Pollack, 1996; Pollack et al., 1995). This is partly related to the overrepresentation of primary diencephalic tumors in this group of LM patients (46%, 6/13) versus the group with only localized disease (19%, 100/515). Also, the higher long-term morbidity of the LM patients was presumably secondary to more extensive radiation (craniospinal), as well as to the presence of dissemination itself. Historically, patients with primary hypothalamic tumors have greater morbidity than LGGs in other locations (Scott and Mickle, 1987).

The median overall survival of our group of children with LM at diagnosis and those in the literature combined—33 patients—is 48+ months (range, 5+ to 175+ months), 5 of whom died. The median overall survival from the time of diagnosis of LGN in 33 patients who were noted to have LM only at the time of progression (Givitello et al., 1988; Doireau et al., 1999; Hukin et al., 2002; Mamelak et al., 1994; McCowage et al., 1996) is
59+ months (range, 14+ to 152+ months), 9 of whom died. The median time to the development of LM in this group of patients is 39 months (range, 8 to 93 months). The cases published to date support our observation that long-standing responses to adjuvant therapy, as well as long-term survival, are possible in LGN patients with LM following administration of adjuvant therapy.

There are several recognizable limitations of this retrospective study. (1) As patients with LGN were not routinely staged at our institution, patients with asymptomatic dissemination in the absence of regional metastases will have been missed and may have been identified only at the time of progression. (2) The advancement in MRI technology may have increased the recognition of LM in recent years. (3) It would have been preferable to confirm MRI evidence of dissemination by cytology or biopsy in all cases; however, in the presence of bulky metastatic disease the morbidity associated with an additional biopsy may not be warranted. (4) Over the 14 years, our management of this entity was modified by evolving treatment strategies. (5) The follow-up in our small series of LM patients is relatively short; this can be addressed by a brief update publication of these patients in 5 or 10 years.

The underlying pathogenesis of LM in patients with LGN is unclear. There are no distinctive microscopic features that suggest these tumors should behave any differently than those without LM. The development of LM may be related to different cytogenetic and molecular factors (Bourdon et al., 1983; Brooks et al., 1994; Jaworski et al., 1996). Increased activity of certain growth factors or adhesion molecules modulating the degree of proliferation and migration may also contribute to the development of metastases (Claffey and Robinson, 1996; De Vries et al., 1992; Edvardsen et al., 1993). It would be of interest to examine the proliferative indices of these tumors (Di et al., 1997; Giese et al., 1996). We are presently examining some of the factors that may play a role in the dissemination of these tumors.

Conclusions

On the basis of this experience, we suggest that caregivers of children with LGN consider the remote possibility of LM when evaluating these patients at the time of diagnosis. The 3% frequency of LM in our series most likely underestimates the true incidence, which will remain unknown in the absence of routine staging. Although the low frequency in this series does not necessarily imply that all patients with newly diagnosed LGN should have routine staging by MRI and CSF examination, we recommend that staging be considered in selected patients, such as those with otherwise unexplained hydrocephalus or clinical suggestion of remote metastases. For optimum treatment planning, we strongly urge that staging be considered, particularly in young patients, prior to initiating adjuvant therapy. The presence of LM requires consideration of a conservative surgical approach; chemotherapy may be a reasonable initial intervention. It would appear that LGNs with LM might behave in an indolent fashion, so that delay of diagnosis and therapy may not be a major disadvantage to the patient in terms of overall survival. However, early diagnosis may be important in terms of reducing disease-related morbidity, influencing adjuvant therapy decisions and the surgical approach. Future studies should be directed at evaluating the pathogenesis of dissemination in these tumors and prospective randomized clinical trials.

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References


