Spinal cord pilocytic astrocytoma with leptomeningeal dissemination to the brain

Case report and review of the literature

TAYLOR J. ABEL, B.S., ABHINEET CHOWDHARY, M.D., MAHESH THAPA, M.D., JOE C. RUTLEDGE, M.D., J. RUSSELL GEYER, M.D., JEFFREY OJEMANN, M.D., AND ANTHONY M. AVELLINO, M.D.

Departments of Neurological Surgery, Radiology, and Laboratory Medicine, Division of Hematology/Oncology, Children’s Hospital and Regional Medical Center, University of Washington School of Medicine, Seattle, Washington

✓Leptomeningeal dissemination of low-grade spinal cord gliomas is an uncommon event. The authors report a unique case of leptomeningeal dissemination of a spinal cord pilocytic astrocytoma (PCA) to the intracranial cerebral subarachnoid spaces in a child. A 2-year-old boy presented with a loss of balance and the inability to walk or stand. An intradural intramedullary spinal cord tumor was identified, and the lesion was subtotally resected and diagnosed by the pathology department to be a PCA. Subsequently, the patient had recurrences of the intradural intramedullary tumor at 6 months and 2 years after his original presentation. He underwent a repeated resection of the recurrent tumor and fenestration of an associated syrinx on both occasions. The pathological characteristics of the resected tumor remained consistent with those of a PCA. Postoperative imaging after his last surgery revealed diffuse intracranial leptomeningeal dissemination into the cisternal space surrounding the midbrain, the suprasellar region, and the internal auditory canal, as well as nodular subarachnoid disease in the upper cervical region. The patient then underwent chemotherapy, and total spine magnetic resonance (MR) imaging 2 months later demonstrated stability in the size of the spinal cord tumor and a decrease in the associated syrinx. However, an MR image of the head demonstrated two new areas of supratentorial subarachnoid leptomeningeal spread of the primary spinal cord tumor at the 2-month follow-up examination. At the 6-month follow-up examination, MR imaging of the head and spine demonstrated stable metastatic disease. This case illustrates a unique instance of supratentorial leptomeningeal dissemination of an intramedullary spinal cord PCA in a child.

KEY WORDS • pilocytic astrocytoma • leptomeningeal dissemination • glioma • recurrent disease • pediatric neurosurgery

Pilocytic astrocytoma is the most common CNS astrocytoma in the pediatric population, representing approximately 30% of all primary brain tumors in children. These low-grade gliomas are usually benign and rarely spread along the neuraxis. They are known to arise most commonly in the thalamus and cerebellum, but can be found anywhere astrocytes are present, including the cerebral hemispheres, hypothalamus, brainstem, optic nerve, and spinal cord. Magnetic resonance imaging usually reveals a well-circumscribed tumor that enhances intensely with the administration of gadolinium. Intramedullary spinal cord PCAs are infrequent, however, representing approximately 9% of cases of PCA.

In rare instances, brain and more rarely spinal cord PCAs have been reported to demonstrate aggressive behavior and are associated with metastatic dissemination to the leptomeninges. Leptomeningeal dissemination of primary CNS tumors in children usually occurs in ependymomas, germ-cell tumors, neuroectodermal tumors, and high-grade gliomas. Leptomeningeal dissemination from low-grade gliomas is less common and has been estimated to occur in 4 to 12% of all cases. A review of the literature on PCA with leptomeningeal dissemination in children revealed fewer than 40 reported cases; the majority were characterized by metastasis of the tumor from the brain to the spinal column via intracranial subarachnoid pathways. We describe the unique case of a 4-year-old boy who har-
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bored a primary spinal cord intradural intramedullary PCA that disseminated intracranially to the leptomeninges. Leptomeningeal dissemination was observed in the supratentorial subarachnoid regions. A review of the literature on low-grade gliomas of the spinal cord revealed few cases of primary spinal PCA with intracranial dissemination. 9,25,27

Case Report

First Presentation and Treatment. This 4-year-old boy initially presented to the emergency department at 2 years of age with a brief history of unsteadiness and loss of balance, which progressed to an inability to walk or stand. Total spine MR imaging revealed an intradural intramedullary spinal cord tumor that extended from C-7 to T-10 (Fig. 1 left). A cranial MR image obtained at that time failed to demonstrate any intracranial lesions (Fig. 1 right). A C6–T11 laminectomy with laminoplasty was performed, and the tumor was subtotally resected. The tumor appeared to have infiltrated the spinal cord in all regions, and a subtotal resection was achieved as noted on postoperative MR imaging. Pathological examination demonstrated a PCA with a few Rosenthal fibers, absent mitotic figures, and a Ki 67 labeling index of less than 1%. Within weeks after discharge from the hospital, the patient’s neurological symptoms improved, and he was able to walk with minimal assistance.

Second Presentation and Treatment. Six months postoperatively, the patient was seen in our clinic with a 2-week history of unsteadiness and loss of balance as well as a 2-day history of an inability to stand or walk. A neurological examination performed at this time revealed Grade 3/5 strength in the muscles of both of his lower extremities. A total spine MR image revealed an enhancing lesion that extended from T-2 to T-7 and an increased size of the associated syrinx (Fig. 2). Because the patient’s neurological condition deteriorated, the spinal cord tumor appeared to enlarge, and an associated syrinx was noted, the patient was immediately taken to the operating room to undergo subtotal resection of the recurrent spinal cord tumor and fenestration of the associated syrinx. The pathological findings were consistent with a PCA (Fig. 3). The microcytic change was focal. Calcifications and an angiocentric pattern were absent. Rosenthal fibers and eosinophilic granular bodies were sparse, but present. The tumor infiltrated normal spinal cord. The patient’s neurological bilateral lower-extremity function improved within a month, and he was able to walk with assistance. Approximately 3 months after the second operation, MR imaging revealed a slight increase in nodular enhancement from T-3 to T-7. However, the patient’s neurological examination revealed an improvement in function.

Third Presentation and Treatment. Two years after the second tumor resection, the patient suffered decreasing bilateral leg function. Total spine MR imaging revealed the development of a syrinx in the thoracic region, but it did not demonstrate an increase in the size of the spinal cord tumor. We then fenestrated the thoracic syrinx and further debulked the residual tumor. The pathological characteristics of the...
resected tumor remained consistent with those of a PCA, and there was no evidence of the lesion degenerating to a more malignant stage. Rosenthal fibers were prominent, and the myxoid change was minimal. Postoperatively, the child’s lower-extremity strength was improved, and he was able to walk with the aid of a walker. Head MR imaging performed immediately postoperatively demonstrated diffuse intracranial leptomeningeal dissemination of the intramedullary spinal cord tumor to the cisternal space surrounding the midbrain and into the suprasellar region, as well as extension into the auditory canal (Fig. 4). One week postoperatively, he commenced a chemotherapy regimen consisting of carboplatin and vincristine. Total spine MR imaging performed 2 months later demonstrated stability of the spinal cord tumor. However, head MR imaging demonstrated two new areas of supratentorial subarachnoid leptomeningeal spread. Six months postoperatively, hydrocephalus and associated mild ventriculomegaly developed in the child, and a lumbar puncture revealed a normal intracranial pressure. Magnetic resonance imaging of the head and spine at this time demonstrated stable metastasis of the tumor. The patient is currently in the maintenance portion of his chemotherapy regimen.

Discussion

Leptomeningeal Dissemination

In this report, we describe the case of a 2-year-old boy who presented with an intramedullary spinal cord PCA that, after three surgeries, was found to have spread to the brain through the leptomeninges. This case adds to the few reports in the literature of a primary spinal PCA that disseminated intracranially.

Intramedullary spinal cord tumors are uncommon in children, representing approximately 5% of all primary CNS neoplasms. Pilocytic astrocytomas are the most frequent pediatric CNS tumors, and approximately 9% of all PCAs are found in the spinal cord. These lesions are known to be low-grade, slow-growing neoplasms that normally have a high rate of cure (80–90%) after gross-total resection. Infrequently, however, intracranial PCAs can behave more aggressively and undergo metastatic transformation or leptomeningeal spread. The incidence of leptomeningeal spread of intracranial low-grade tumors is rare; it is estimated to be 5% at presentation and 7 to 10% with disease progression. However, the number of diagnosed cases is increasing with the use of MR imaging.

Leptomeningeal spread of a primary CNS tumor was first described in the 1800s. Since then, there have been numerous reports of leptomeningeal dissemination of a variety
of tumors, the vast majority of which are classified as aggressive. The pathological condition is thought to develop when tumor cells are located close to the CSF. Once tumor cells are able to enter the CSF, they may disseminate to all areas of the CNS. Normally, they seem to follow the pattern of CSF flow. The most common areas of leptomeningeal dissemination are the basilar cisterns, sylvian fissures, and cauda equina, most likely because of both gravity and the slower rate of CSF flow in these areas. In the present case, however, tumor dissemination seemed to be contrary to the pattern of CSF flow. No dissemination was seen caudal to the primary spinal cord tumor; rather dissemination occurred cranially, both in the suprasellar cistern and the supratentorial subarachnoid space, probably due to spread from within the leptomeninges of the cervical cord region.

Leptomeningeal dissemination of low-grade gliomas, including PCAs, is an area of research and debate. Why a small percentage of seemingly low-grade tumors act in an aggressive manner, contrary to their pathological characteristics, remains puzzling. In early theories it was speculated that resections and therefore tumor manipulation contributed to dissemination through the exposure of tumor cells to the CSF. Although this mechanism may play a role in some cases, it is most likely not the primary origin, given that there are numerous reports of dissemination at initial presentation. Furthermore, studies have failed to demonstrate any correlation between dissemination and resection. Authors of other reports on leptomeningeal dissemination of low-grade gliomas have paid particular attention to the pathological characteristics of the tumor, and they often use unusual terminology to describe the lesions, such as microcystic astrocytoma or astrocytoma further unspecified. Tihan, et al., described a subset of low-grade gliomas that have a higher tendency to undergo dissemination, which they termed “monomorphous pilomyxoid tumor.” They described the lesions as having many of the same features as a PCA, but also having a more monomorphous and myxoid character as well as no Rosenthal fibers or eosinophilic granular bodies. These tumors occur most commonly in infants and young children. They are primarily seen in the hypothalamic–chiasmatic region, but have recently been reported to occur in the spine as well. Particular care should be taken when defining the pathological features of the low-grade tumor specimens in that the characteristics may yield insight into defining subsets of gliomas that have a higher tendency to disseminate. In this case, however, the patient presented with and continued having a tumor that had features more in keeping with a PCA than a pilomyxoid astrocytoma. The lesion never underwent malignant transformation to a more aggressive histology, which are unusual characteristics for a PCA, nor did it display the characteristics of a monomorphous pilomyxoid tumor.

Standard histological techniques may not be sufficient to predict the progression of low-grade gliomas to dissemination. Biological markers may be on the horizon to help predict the clinical outcome of these lesions. Recent studies comparing the molecular genetics of pediatric low-grade gliomas with and without leptomeningeal dissemination yielded interesting results. Comparative genomic hybridization revealed that the majority of disseminated low-grade gliomas examined had amplification of the short arm of chromosome 7. The studies went on to describe using in situ hybridization and immunohistochemical analysis for ampli-
fication of the EGFR gene located on the short arm of chromosome 7 in low-grade gliomas with dissemination compared with those without. The EGFR receptor is a transmembrane glycoprotein that is a tyrosine kinase receptor. The binding of epidermal growth factor to its receptor leads to autophosphorylation and activation of numerous signaling cascades including those involved in cell proliferation, as well as invasiveness through the expression of metalloproteinases and adhesion molecules. Furthermore, it has been demonstrated that the EGFR is also expressed in high-grade gliomas. Potentially, overexpression of EGFR could cause low-grade gliomas, or perhaps a subset of cells within the tumor, to act more aggressively, and lead to leptomeningeal dissemination. Additionally, there are known inhibitors of the EGFR, which may be useful as adjunct therapeutics.

Further studies into the differences between low-grade gliomas with and without dissemination will provide greater insight into the pathobiology of this disease as well as more biological markers to guide clinicians to better diagnostic, prognostic, and therapeutic assessments.

Review of the Literature

A literature review revealed numerous cases of spinal cord glioma with intracranial dissemination. In 1987, Johnson and Schwarz reported the case of a 9-year-old girl. In 1992, the first resection was performed for recurrence, and the histological findings from this operation revealed a transformation to a WHO Grade II astrocytoma. The CSF studies obtained at this time revealed polymorphic giant tumor cells of a GBM. Soon after, the patient died of cardiovascular insufficiency; a postmortem examination demonstrated pronounced leptomeningeal dissemination of the astrocytoma with subarachnoid infiltrations along the basal cerebellum and ventral brainstem. The spinal cord was surrounded by a cuff of tumor growth that infiltrated the cauda equina. None of this tumor extended outside of the CNS.

In 2001, Ng, et al., reported the case of a 9-year-old girl with a PCA in her spinal cord with intracranial leptomeningeal dissemination. On initial presentation MR images obtained in this child showed an intramedullary cervical spinal cord tumor that extended from C-5 to C-7. Cranial MR imaging did not show any abnormalities in the brain. Histological materials taken from the first resection demonstrated a PCA with well-differentiated bipolar cells and few Rosenthal fibers. There was no evidence of mitosis or endothelial proliferation. Two and a half years after surgery the child became symptomatic, and MR imaging demonstrated residual cervical spine tumor as well as tumor spread to both the sylvian fissures and the areas surrounding the cerebellar sulci and brainstem. A craniotomy was performed to resect the tumor, which had spread intracranially, and the postoperative histological report was consistent with spread of the spinal PCA via the leptomeninges. The histological samples exhibited differentiated spindle cells and Rosenthal fibers.

Most recently, in 2004, Peraud, et al., reported the case of a 14-year-old boy who presented with an intramedullary spinal cord tumor at the T11–12 level. No intracranial lesion was present at that time; the histological diagnosis made after the first resection was an atypical PCA (WHO Grade II). Rosenthal fibers and multinuclear tumor cells were not apparent in the histological samples. After subsequent MR images demonstrated a slight increase in tumor size, a second resection of the tumor was performed; the histological findings at this time were consistent with a low-grade astrocytoma (WHO Grade II). Four years after the initial presentation, MR imaging revealed contrast-enhancing lesions around the third and fourth ventricles and recurrence of the spinal cord tumor at the initial resection site. A pathological evaluation was consistent with an anaplastic PCA (WHO Grade III).

An interesting aspect of our case is that neurons were present in all of the biopsy samples obtained at surgery. Al-

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Primary Location</th>
<th>Mech of Spread</th>
<th>Pathological Finding</th>
</tr>
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<tbody>
<tr>
<td>Claus, et al., 1995</td>
<td>43, M</td>
<td>conus medullaris</td>
<td>LM</td>
<td>Grade I PCA, Grade II astrocytoma</td>
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<tr>
<td>Ng, et al., 2001</td>
<td>9, F</td>
<td>C5–7</td>
<td>LM</td>
<td>PCA, PCA</td>
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<tr>
<td>Peraud, et al., 2004</td>
<td>14, F</td>
<td>T11–12</td>
<td>LM</td>
<td>Grade II atypical PCA, Grade III anaplastic PCA</td>
</tr>
<tr>
<td>present case</td>
<td>2, M</td>
<td>C7–T10</td>
<td>LM</td>
<td>PCA, PCA</td>
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* LM = via the leptomeninges; mech = mechanism.
though the distribution and morphological characteristics of the neurons in these samples remains consistent with infiltration, the presence of neurons raises the unlikely possibility that the tumor we observed in this case is actually a ganglioglioma. Gangliogliomas are well-demarcated, slow-growing tumors that typically have a benign clinical course. The malignant transformation and dissemination of gangliogliomas is a rare occurrence and only a few cases have been reported in the literature.\textsuperscript{12,24,41} Mittler, et al.,\textsuperscript{24} reported the case of a 21-year-old man with an intramedullary ganglioglioma, which after a second resection displayed histological characteristics of an anaplastic glial neoplasm. Biopsy samples demonstrated differentiation of both ependymal and astrocytic cell lines. This lesion was initially diagnosed as a glial–neuronal hamartoma/ganglioma, and the authors were uncertain as to whether the malignant development represented malignant transformation of the original lesion or an entirely separate lesion. In another report, Di Patre, et al.,\textsuperscript{12} described the case of a 42-year-old woman with a T7–9 intramedullary ganglioglioma which, after a second resection displayed histological characteristics of an anaplastic glial neoplasm. Biopsy samples demonstrated differentiation of both ependymal and astrocytic cell lines. This lesion was initially diagnosed as a glial–neuronal hamartoma/ganglioma, and the authors were uncertain as to whether the malignant development represented malignant transformation of the original lesion or an entirely separate lesion. In another report, Di Patre, et al.,\textsuperscript{12} described the case of a 42-year-old woman with a T7–9 intramedullary ganglioglioma which, after a second resection, exhibited malignant features. After the first resection, this tumor demonstrated features characteristic of a ganglioglioma, and both ganglionic and astrocytic cells were present. One and a half years after this surgery, tumor recurrence noted from T-5 to T-10 prompted a second resection. Histological samples obtained during this operation demonstrated a highly cellular tumor with a high nucleocyttoplasmic ratio and brisk mitotic activity consistent with an anaplastic small cell glioma. We believe that our case represents malignant dissemination of an intramedullary PCA, although the presence of neurons in the biopsy samples raises the possibility that the case represents dissemination of a ganglioglioma. This possibility is unlikely, however, because the distribution of neurons is consistent with infiltration of the spinal cord rather than ganglioglioma.

**Conclusions**

In this report we described a child with a classic PCA in the spinal cord that, after three resections, exhibited leptomeningeal dissemination supratentorially. This case is unique in that a classic spinal cord PCA disseminated to the brain via the leptomeninges. Supratentorial dissemination of a primary intramedullary PCA is a rare occurrence; only a few cases have been reported in the literature. Although histological findings in all the biopsy samples remain consistent with a classic PCA, the identity of the tumor within the supratentorial leptomeninges remains uncertain.

**References**


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