Intracranial metastases from malignant spinal-cord astrocytoma

Case report

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A patient with postoperative intracranial seeding from a malignant spinal-cord astrocytoma is presented. This case is compared with 17 previously cited cases of intracranial dissemination from spinal-cord astrocytoma. Factors associated with tumor dissemination include histological malignancy, proximity of the tumor to cerebrospinal fluid (CSF) pathways, and surgical manipulation. Hydrocephalus with infiltration of the basal cisterns also appears to be a consistent feature in these patients. Cytological studies of the CSF in this and previous cases were noted to be misleading, whereas intravenous contrast-enhanced cranial computerized tomography was invaluable for diagnosis of tumor dissemination in each case. Prophylactic irradiation of the entire neuraxis may limit intracranial metastases from malignant astrocytomas of the spinal cord.

KEY WORDS • astrocytoma • spinal-cord neoplasm • metastases

Spinal-cord astrocytomas are rare, comprising only 1% of all primary central nervous system tumors.23 Malignant astrocytomas grades III and IV account for only 7.5% of intramedullary spinal-cord gliomas occurring in all age groups and for as few as 1.2% of primary intramedullary tumors in children.1,6,9,10,12,14,23,24,29 Because of their rarity, the biological behavior of malignant spinal-cord astrocytomas has not been well delineated. Cooper and Epstein2 alluded to this in a recent report of 29 intramedullary spinal-cord tumors in adults. Three of their patients had malignant astrocytomas, and all died as “a result of tumor dissemination throughout the neuraxis or progressive involvement of the upper cervical spinal cord with respiratory failure.”

We report a case of postoperative intraventricular metastases from a primary malignant spinal-cord astrocytoma. It is the first case in which dissemination and progression of disease is well documented by cranial computerized tomography (CT). The pathophysiology of tumor dissemination and its therapeutic ramifications are discussed.

Case Report

This 8-year-old girl was brought for evaluation of a 3-month history of severe back pain and a 1-month history of progressive right leg weakness. A more recent but poorly defined history of occasional urinary incontinence was also elicited. Neurological examination revealed a mild spastic paraparesis, worse on the right, with partial loss of proprioception and sensation to pinprick on the right below the L-1 dermatome. Plain x-ray films of the spine were remarkable only for slight curvature of the thoracolumbar spine to the right. Metrizamide myelography followed by CT scanning demonstrated an expanded conus medullaris. Concurrent cranial CT showed no intracranial lesions (Fig. 1). Analysis of the cerebrospinal fluid (CSF) for protein and sugar levels and cell count was normal. Cytology was not performed. A thoracolumbar en bloc laminotomy at T11–L3 exposed an enlarged conus with a thin sheet of gray vascular tumor emerging from the anterolateral aspect of the conus, streaming dorsally beneath the pia. Eighty percent of the tumor was removed through a midline myelotomy. Microscopic dissection revealed extensive infiltration of the adjacent cord substance. The pathological diagnosis was astrocytoma, Kernohan grade 3,16 based on astroglial hypercellularity and hyperchromatism. Although nuclear palisading was present, no necrosis or endothelial proliferation was evident (Fig. 2).

Postoperatively, the patient had relief from back pain...
but there was increased neurological deficit with transient loss of bladder and bowel control. A total dose of 5100 rads divided over 6 weeks was delivered to the T6–L3 area through direct posterior and posterior oblique ports. The patient's gait steadily improved and sphincter disturbances resolved.

Four months after surgery the patient was reevaluated because of malaise and intermittent frontal and vertex headaches which were occasionally associated with vomiting. Although the paraparesis had continued to improve, papilledema and impaired ocular convergence were noted on examination. A CT scan revealed mild hydrocephalus with homogeneous hyperdense contrast-enhancing masses in the left frontal horn, right and left lateral ventricular atria, and fourth ventricle (Fig. 3). Additional therapy was initiated with whole-brain irradiation of 5040 rads in 28 fractions. The lateral and fourth ventricular tumors received boosts of 540 rads.

Two months after completion of radiation therapy, CT demonstrated ventricular dilatation and enlargement of the mass in the fourth ventricle. Cytological examination of the CSF demonstrated no malignant cells. The patient was started on an "8-in-1" chemotherapeutic regimen, consisting of a 1-day battery of eight agents (vincristine, 1-(2-chloroethyl)-3-cyclohexyl-l-nitrosourea (CCNU), procarbazine, hydroxyurea, cisplatin, cytosine arabinoside, methyl prednisolone, and cyclophosphamide) to be given every 3 weeks (Protocol CCG-091). She tolerated two doses of this treatment regimen only marginally with repeated vomiting. A cranial CT 2 weeks after her second course of treatment showed no response to the therapy. Because of intractable vomiting, the patient underwent suboccipital craniectomy and subtotal excision of the fourth ventricular tumor. The tumor extensively infiltrated the vermis, right cerebellar hemisphere, and floor of the fourth ventricle. Pathological diagnosis was again astrocytoma grade 3, with marked nuclear pleomorphism, irregular areas of necrosis, and palisading of tumor cells. Mitotic activity and endothelial proliferation were not seen (Fig. 4). Tumor tissue removed from the fourth ventricle failed to grow in tissue culture (courtesy of Dr. Paul Kornblith). The hydrocephalus and intractable vomiting resolved.

Six weeks later, vomiting recurred in association with incapacitating headaches. A CT scan demonstrated a right subdural hygroma and recurrent hydrocephalus. Evacuation of the subdural hygroma only transiently resolved vomiting and headache. Complete symptomatic relief was achieved following CSF diversion into the peritoneal cavity. Despite a course of spiromustine (Protocol NSC 172112), her paraparesis worsened and she developed progressive quadriplegia and respiratory insufficiency over a 48-hour period. She died 14 months after diagnosis. Permission for postmortem examination was not granted.

**Discussion**

In addition to the present patient, 17 cases of spinal-cord astrocytoma with intracranial dissemination have been reported since 1908 (Table 1). Ten cases were malignant; in four other cases the biopsied portion of the primary tumor was grade 2, but...
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The metastases were grade 4. Ten (59%) cases involved the conus. One case was cervical and four were thoracic in location. The average age of the patients was 23 years, ranging from 11 to 45 years (in three the age was not recorded). The interval between diagnosis of the cord tumor and intracranial dissemination ranged from 1 week to 11 months, averaging 6 months. Surgical biopsy of the spinal-cord tumor preceded intracranial dissemination in 13 cases. The other four patients were reported for the pathology only, with no mention of surgery. Twelve patients received radiation therapy before dissemination, three were not irradiated, and clinical information was not recorded in two. Hydrocephalus was demonstrated by ventriculography or autopsy in 11 cases; in the remaining six cases ventricular size was not reported. Local pial invasion by the primary cord tumor was common to all reported cases.

In each of the 17 cases, the symptoms and signs of

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Primary Site of Tumor</th>
<th>Histological Grade</th>
<th>Surgery</th>
<th>Interval: Surgery to Dissemination</th>
<th>Radiation Therapy</th>
<th>Basal Cistern Infiltration</th>
<th>Hydrocephalus</th>
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<tr>
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<td>child</td>
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<td>1 wk</td>
<td>no</td>
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<td>11 mos</td>
<td>yes</td>
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<td>11, F</td>
<td>cervical</td>
<td>4</td>
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<td>no</td>
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<td>3 mos</td>
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* Histological grade according to Kernohan, et al. NR = not recorded; NA = not applicable.
spinal-cord tumor preceded those of the intracranial lesions. Our case report is the first to document the absence of intracranial lesions at the time of primary tumor diagnosis. Proximity to the CSF pathway, malignant histology, and hydrocephalus are features common to all cases and suggest the following pathophysiological sequence: dispersion of tumor cells through the subarachnoid space, obliteration of the basal cisterns, development of hydrocephalus, ventricular reflux of tumor cells, and implantation of tumor on the walls of the ventricles.

If a tumor is exposed to the CSF pathway, tumor cells will follow the pathway of bulk CSF flow. Thus, cranial tumors (especially posterior fossa tumors) will seed the spine assisted by gravity, and spinal tumors will seed cephalad with the CSF flow toward the arachnoid granulations.

The risk of operative contamination of wounds with tumor cells has long been a concern among surgeons. Smith, et al., 30 studied 111 general surgical patients prospectively and found no statistically significant correlation between positive cytological findings from intraoperative wound washing and incidence or rate of local recurrence. Cytological examination of perioperative CSF samples may be no better as a predictor of postoperative tumor dissemination for the neurosurgeon. Wilkins and Odom 32 studied perioperative changes in CSF cytology in craniotomy patients and found that surgical manipulation did not increase tumor cell shedding for either benign or malignant gliomas. In addition, they noted a similar incidence in the CSF of tumor cells from both benign and malignant gliomas preoperatively. However, their results are inconclusive because analysis was performed on the number of individual specimens rather than on the number of patients. Balhuizen, et al., 3 looked at this issue more recently and did find a substantial increase in postoperative positive cytology in patients with benign intracranial astrocytomas but not in malignant intracranial gliomas. As in the study by Wilkins and Odom, no correlation was made between postoperative positive CSF cytology and postoperative tumor dissemination. Furthermore, a high incidence of false negative CSF cytology has been reported in cases of biopsy- or autopsy-proven dissemination of astrocytoma of cerebral (33%), 33 cerebellar (100%), 17 brain-stem (33% to 75%), 15,21 or spinal cord (50%) 13 origin. In our own case, cytological examination revealed no malignant cells in the CSF at the time the intraventricular metastases were discovered. The risk of astrocytoma cells establishing distant implants once shed into the CSF remains enigmatic. Tumor cell kinetics and host resistance undoubtedly play a role.

As early as 1931, Cairns and Russell 4 recommended whole-axis irradiation in treating malignant cord tumors. The most convincing argument for whole-axis postoperative irradiation was made by Salazar. 26 He reported 13 cases of malignant cerebellar astrocytoma in children. Six patients were treated with subtotal excision and cranial irradiation only. Five of the six patients developed spinal metastases; the mean period of survival was 10 months. Seven subsequent patients were treated with subtotal excision and whole-axis irradiation; all remained free of spinal metastases during the 1- to 4-year follow-up period. The median survival time in this group was 48 months. Further review of the literature and our own experience with this case supports this view.

Conclusions
Malignant astrocytomas of the spinal cord are rare in adults and even less common in children. The incidence of intracranial metastases from such malignant tumors is not known but may be higher than expected since malignant astrocytomas of the spinal cord are so rare. Malignant tumors that have access to the subarachnoid space disperse according to their point of origin within the CSF pathway. Malignant cerebral astrocytomas will seed locally to the leptomeninges and caudad to the spinal subarachnoid space by gravity. Similarly, malignant astrocytomas of cerebellar or brain-stem origin will metastasize to the spinal subarachnoid space. Metastases from malignant astrocytomas of the spinal cord will follow the flow of CSF back toward the arachnoid granulations. In addition to malignant histology and direct exposure to the subarachnoid space, spinocranial dispersion is associated with basal cistern obliteration, hydrocephalus, and intraventricular reflux of the tumor particles. Surgical contamination of the subarachnoid space is less important, and CSF cytology is unreliable in these patients for excluding subarachnoid and intraventricular metastases. The diagnosis of malignant astrocytoma of the spinal cord warrants complete radiographic examination of the neural axis. Despite the absence of dissemination on these initial studies, irradiation of the whole neuraxis must be strongly considered in the treatment plan.

References
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