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Malignant astrocytomas of the spinal cord

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✓ The authors review their experience with the operative management of 19 consecutive cases of malignant astrocytoma of the spinal cord. There was a male to female ratio of 1.1:1, and the median age of the population was 14 years (range 1 to 32 years). The median duration of symptoms prior to definitive diagnosis was 7 weeks. Radical excision was carried out in all cases, with 18 patients (95%) receiving radiotherapy and 10 patients (53%) receiving chemotherapy as well.

To date, 15 (79%) of the 19 patients in this series have died, with a median survival period of 6 months following surgery. No patient improved after operation. Hydrocephalus was present in 11 patients (58%), seven of whom underwent ventricular shunting procedures. Dissemination of disease was found in 11 patients (58%). Extraneural metastases did not occur in the absence of a ventricular shunt. The authors conclude that malignant astrocytomas of the spinal cord are heralded by a short history followed by rapid neurological deterioration and usually death. The rationale for operation is discussed, and an aggressive approach utilizing adjuvant therapy directed at the entire neuraxis is suggested.

KEY WORDS • **astrocytoma** • **glioblastoma multiforme** • **spinal cord neoplasm**

BECAUSE malignant astrocytomas of the spinal cord occur so infrequently, little has been written about their biological behavior. These tumors represent only a small subset of yet another distinctly uncommon neoplasm, the intramedullary spinal cord astrocytoma. Intramedullary spinal cord astrocytomas altogether account for only 6% to 8% of all primary spinal cord tumors.[4,25,26] The vast majority of these astrocytomas are benign neoplasms, and recent reports have shown that radical surgery can often be associated with improvement in neurological function and possibly an increase in survival time.[5,6,11–14,18,28,29]

Malignant astrocytomas (Kernohan grades III and IV[23]) comprise only 7.5% of all intramedullary spinal cord gliomas,[22,27] and are even less common in children.[7,8,15–17,19,21] There is general agreement that malignant intramedullary spinal cord astrocytomas, like their intracranial couterparts, carry an ominous prognosis. This report details the authors' experience with 19 consecutive cases of malignant astrocytomas of the spinal cord.

Clinical Material and Methods

Patient Population

One hundred seventy patients underwent operation for intramedullary astrocytoma of the spinal cord in the 6 years between July, 1981, and August, 1987. Of these, 19 patients (11%) harbored tumors that were histologically malignant (grade III or IV) and these patients form the basis of the present study.

There were 10 male and nine female patients whose ages ranged from 1 to 32 years, with a median age of 14 years. Tumors were located in the cervical cord in 12 patients and in the thoracic cord in seven patients; of the latter, two were midthoracic and five were at the level of the conus medullaris. Symptoms and signs were often referable to the site of solid tumor, as was true for our series of benign intramedullary astrocytomas. Symptoms consisted of posterior midline pain, numbness and paresthesias, and weakness below the level of the tumor; four patients had headache at the time of presentation and each was ultimately found to have hydrocephalus (Table 1).

Functional motor impairment upon presentation was ranked on a scale of I to IV, with Grade I representing a patient having minimal or no functional impairment and Grade IV representing a patient who was paraplegic or quadriplegic (Table 2). Ten patients presented with no motor deficit or only mild impairment (Grade I or II), and nine patients had moderate or severe deficits at the time of presentation (Grade III or IV). Eight patients (42%) had sphincter dysfunction at the time of initial examination.

TABLE 1

Presenting symptoms in 19 patients

Symptom	No. of Cases
weakness	15
pain	13
numbness & paresthesias	4
headache	4

TABLE 2

Scale of functional motor impairment

Grade	Description
I	intact or minimal neurological deficit, no functional impairment
II	mild neurological deficit, ambulating without braces or aids, no functional impairment
III	moderate neurological deficit, ambulating with braces and/or aids, significant functional impairment
IV	quadriplegic or paraplegic, wheelchair-dependent, significant functional impairment

The duration of symptoms from onset to the time of definitive diagnosis ranged from 1 week to $8\frac{1}{2}$ years, with a median duration of 7 weeks. In three patients there was a subacute course with symptoms lasting for 48, 84, and 102 months prior to their present operation. Each of these three patients was found to have a malignant tumor on reexploration, having initially presented with a low-grade astrocytoma at an earlier operation. Excluding this small subset yielded a median duration of symptoms of only 5 weeks for the present series.

Neurodiagnostic Studies

Patients were evaluated with myelography using water-soluble contrast material, followed by computerized tomography (CT) scanning or by magnetic resonance (MR) imaging. Our present protocol is to begin with a sagittal MR study to delineate the region of spinal cord widening, with further axial images obtained through the area of interest. Multiecho sequences are helpful, but not completely reliable, in differentiating solid tumor from rostral and caudal cysts.

When myelography was performed it was followed by CT at 10-mm intervals through the region of spinal cord widening. A second "delayed" CT scan was obtained 12 to 24 hours later to further define rostral and caudal tumor-related cysts. These cyst cavities, unlike the regions of solid tumor, often showed uptake of the contrast material on delayed CT.

Spinal cord angiography was not performed in any of the cases. Transcutaneous ultrasonography was used in certain cases in which patients had already undergone laminectomy, but the major application of ultrasound was to provide intraoperative transdural localization of solid tumor and tumor-associated cysts.

Surgical Technique

Operations were carried out with the patient in the prone position. Somatosensory evoked potentials were monitored, utilizing a system that updated information every few seconds in order to provide rapid feedback to the surgeon. Laminectomy was performed over the region suspected of harboring solid tumor on the basis of preoperative neurodiagnostic testing. Prior to dural incision, intraoperative ultrasound proved to be highly accurate in defining the length of tumor and the presence or absence of rostral and caudal cysts. After dural incision, the operating microscope was brought into the field and a midline myelotomy made using a carbon dioxide laser at low wattage. Fine pial retraction sutures were inserted, and a radical cytoreductive tumor removal was carried out with the aid of the Cavitron ultrasonic surgical aspirator and the laser. Rostral and caudal cysts were drained whenever found. Intraoperative ultrasonography was used repeatedly to monitor the extent of tumor removal. The dura was closed primarily whenever possible. All patients received perioperative intravenous methylprednisolone in high doses (15 to 30 mg/kg/day).

Adjunctive Treatment

Twelve patients had previously undergone surgery for either biopsy (nine patients) or subtotal removal of tumor (three patients).

Eighteen of the 19 patients received radiation therapy, six prior to the present operation and 12 subsequent to it. The only patient who did not receive radiation was a girl aged 1 year at the time of operation. Ten of the 12 patients who were irradiated postoperatively received therapy directed at the entire neuraxis with a boost to the tumor bed. One patient who was already incontinent and paraplegic underwent a postoperative "radiocordectomy" with 10,000 rads delivered to the region of the conus medullaris.

Ten patients received chemotherapy following their operation. Drugs used were either 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) or multiagent therapy consisting of prednisone, 1-(2-chloroethyl)-1-nitrosourea (CCNU), and vincristine, or a protocol combining eight drugs in 1 day ("8 in 1" therapy).

Results

Pathological Findings

At surgery, the malignant astrocytomas usually had a reddish or reddish-gray, glassy appearance. Malignant tumors appeared more vascular than their benign counterparts, and the interface with normal spinal cord tended to be more indistinct. On occasion, tumor was visible at surgery on the surface of a widened spinal cord, lying in contiguity with the cerebrospinal fluid (CSF) pathways. The fluid in rostral and caudal cysts was inevitably xanthochromic.

Malignant astrocytomas were defined as grade III or IV according to the classification of Kernohan and

Sayre[23] on the basis of histological examination. Seven tumors were grade III astrocytomas, two tumors were grade III–IV, and 10 were grade IV.

Three patients presented with an indolent course. In each case a low-grade astrocytoma was initially diagnosed by biopsy at a referring hospital. Symptoms lasted from 2 to $8\frac{1}{2}$ years prior to diagnosis of a malignant tumor at the time of the present operation. Two of these patients died within 2 years of this operation; the third is alive at 3 months following surgery.

Clinical Outcome

Fifteen (79%) of the 19 patients in this series have died. The median survival time from operation to death was 6 months with a range of 1 to 28 months. The median survival time from onset of symptoms until death was 11 months with a range of $1\frac{1}{2}$ to 108 months (Table 3). Of the four survivors only two have lived for longer than 1 year postoperatively, each having survived 17 months following surgery. Both of these patients received neuraxis irradiation. One is paraplegic with loss of sphincter function, and the other is ambulatory with a Brown-Séquard syndrome. The overall outcome for patients in this series was dismal. None developed neurological improvement postoperatively and all either died, deteriorated, or remained unchanged.

Eleven (58%) of the 19 patients developed hydrocephalus, and seven of these 11 underwent ventricular shunting procedures. There was a strong tendency for dissemination of disease to occur, with 11 (58%) of the 19 patients showing radiographic or autopsy evidence of tumor dissemination, either local (via subarachnoid pathways) or more distant intracranial involvement (Table 4). Six of the 11 patients with disseminated disease had undergone shunt placement. Only one patient developed extraneural metastases (to the peritoneum and bone), which occurred following ventricular shunt placement.

Complications

There were two cases of wound breakdown. The first occurred in a patient who had undergone two previous biopsies as well as radiotherapy for a cervical tumor prior to the present operation. The other developed in a patient who received a 10,000-rad "radiocordectomy" following the present operation.

Discussion

Malignant astrocytomas make up a small subset of intramedullary spinal cord tumors, and carry a dismal prognosis. Characteristically, there is a short prodrome of only several weeks prior to diagnosis followed by progressive neurological deterioration and death. This is in direct contradistinction to the long indolent course followed by patients harboring "benign" spinal cord astrocytomas, where symptoms have often existed for many months or years prior to diagnosis. Although surgery was generally well tolerated by patients in this series, it clearly did not have the same favorable impact upon their disease as has been true for low-grade astrocytomas of the spinal cord.

TABLE 3

*Summary of clinical course in 19 patients**

Case No.	Age (yrs), Sex	Duration of Symptoms (mos)	Preop Motor Impairment	Tumor Location	Histological Grade	Hydrocephalus	Tumor Dissemination	Postop Follow-Up or Survival Time (mos)	Outcome
1	17, F	1	IV	thoracic	IV	yes	yes	10	dead
2	16, F	10	IV	conus	IV	yes	yes	6	dead
3	27, F	5	II	cervical	III	yes	yes	4	dead
4	8, M	84	II	cervical	III–IV	yes	no	24	dead
5	14, M	$\frac{1}{4}$	IV	cervical	III	yes	yes	6	dead
6	14, M	9	II	conus	IV	yes	yes	4	dead
7	7, M	48	III	thoracic	IV	no	no	12	dead
8	14, F	1	IV	conus	III	yes	yes	28	dead
9	32, M	6	IV	cervical	IV	no	no	5	dead
10	15, M	2	III	conus	III–IV	no	yes	17	dead
11	20, F	13	IV	cervical	III	no	yes	7	dead
12	10, F	1	II	cervical	IV	yes	yes	5	dead
13	4, F	1	II	cervical	IV	no	yes	8	dead
14	19, F	3	I	cervical	III	no	no	17	alive, Brown-Séquard syndrome
15	19, M	1	IV	conus	IV	yes	no	17	alive (plegic), wound problems
16	9, M	$\frac{1}{2}$	II	cervical	IV	yes	yes	1	dead
17	20, M	1	II	cervical	III	yes	no	4	dead
18	1, F	$\frac{3}{4}$	II	cervical	III	no	no	3	alive, unchanged
19	11, M	102	II	cervical	IV	no	no	3	alive, unchanged

* For scale of motor impairment see Table 2. Histological grading according to Kernohan and Sayre.[23]

Fifteen (79%) of our 19 patients with malignant astrocytomas died after a median survival time of only 6 months following operation. Of the four survivors, only two have lived for longer than 1 year. No patient improved following surgery.

Our results suggest a strong propensity for patients with malignant spinal cord astrocytomas to develop hydrocephalus. Eleven patients in this series (58%) developed hydrocephalus and seven of these required ventricular shunt insertion. Patients with tumors of the thoracic cord and conus were as likely to develop hydrocephalus as were those with cervical tumors. This tendency to develop hydrocephalus was unique to patients with malignant astrocytomas and was seen only rarely in our series of low-grade astrocytomas. Previous reports have described intracranial hypertension, hydrocephalus, and papilledema in association with a variety of spinal cord neoplasms,[1,3,30] and it has been suggested that elevated protein levels lead to defective CSF reabsorption. The true cause of hydrocephalus in our patient population remains obscure.

Clearly, there is a striking tendency for patients with malignant spinal cord astrocytomas to develop disseminated disease. This was observed in 58% of our patients. Most commonly, tumor spreads in the subarachnoid space with local or distant involvement of the leptomeninges.[2,9,10,22] This is best explained by the close proximity of malignant glial cells to the CSF pathways. Sometimes tumor was found to already involve the subarachnoid space at the time of surgery. The possibility cannot, however, be excluded that surgery facilitated the disease dissemination by increasing the exposure of malignant cells to the subarachnoid pathways. It is also possible that some cases of distant intracranial spread may instead represent "multicentric glioma." The frequency of central nervous system dissemination is to be contrasted with the rarity of extraneural metastases which in this series did not occur in the absence of a ventricular shunt.

There were three unusual cases in this series in which the patients presented initially with a biopsy-proven low-grade astrocytoma. All had a paucity of symptoms and a long static course with associated scoliosis for 2 or more years. Once the diagnosis of a malignant tumor was made at the present operation it appeared that these patients responded like the rest of those in our series: two are dead and one is living, but only 3 months have elapsed since operation. This phenomenon may be explained by malignant degeneration in a small subset of benign tumors.

Histological grade seems to be a major factor in predicting prognosis in patients with intramedullary spinal cord astrocytomas.[20,24] The results of this study taken together with our series of patients with benign astrocytoma[11,13] appear to confirm this. Furthermore, we have noted that the duration of symptoms prior to definitive diagnosis is also a strong predictor of the potential success or failure of surgery. Excluding rare cases with a long prodrome (discussed above), patients with malignant spinal cord astrocytomas had a characteristically short history and rapid evolution of symptoms. This short presenting history can also sometimes be seen in cases of intramedullary spinal cord ependymomas, usually on the basis of preoperative hemorrhage. In addition to their short history, patients with malignant spinal cord astrocytomas tended to have significant neurological dysfunction at the time of presentation. In our series, 49% had severe functional motor impairment and 42% had sphincter dysfunction at the time of presentation.

In spite of the dismal prognosis associated with malignant spinal cord astrocytomas, we continue to recommend an aggressive approach. Radical surgery is advocated for several reasons: 1) it allows one to confirm the diagnosis, which can be inaccurate due to sampling error following biopsy alone;[5] 2) cytoreductive debulking of the tumor may be an important adjunct to irradiation and chemotherapy; and 3) radical operation has been helpful for pain control, even in patients with a serious fixed neurological deficit.

The major surgical complication encountered was related to wound healing in two patients, and this was presumably due to the effects of radiotherapy. Consequently, previously irradiated wounds are now closed

TABLE 4

Disseminated disease in 11 patients

Case No.	Original Tumor Location	Area of Disease Spread	Documentation	Shunt Placed
1	thoracic	subarachnoid space, brain stem, extraneural	autopsy	yes
2	conus	septum pellucidum	x-ray study	no
3	cervical	brain stem	x-ray study	yes
5	cervical	subarachnoid space, diffuse spinal cord seeding	autopsy	yes
6	conus	intracranial spread	autopsy	yes
8	conus	brain stem, intraventricular	x-ray study	yes
10	conus	subarachnoid space, rostral ascent to cervical cord & intracranial spread	x-ray study	no
11	cervical	subarachnoid space, brain stem	x-ray study	no
12	cervical	subarachnoid space, widespread craniospinal dissemination	x-ray study	yes
13	cervical	subarachnoid space, widespread cord involvement	x-ray study	no
16	cervical	brain stem	autopsy	no

in association with a plastic surgeon. Tension-free musculofascial flaps are mobilized, closed with permanent Prolene sutures, and tested for leakage by injection of saline through a catheter inserted deep to the layer to be tested. This technique has resulted in excellent healing of complicated wounds.[31]

We conclude that malignant spinal cord astrocytoma is as lethal as it is rare. It is characterized by a short prodrome followed by rapid and relentless clinical deterioration, with a strong propensity to disseminate and produce hydrocephalus. Although an aggressive approach including radical cytoreductive surgery, accurate staging, complete neuraxis irradiation, and adjuvant chemotherapy is encouraged, to date we have not been able to favorably alter the outcome of this devastating tumor.

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