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Cerebrospinal metastases in malignant childhood astrocytomas

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Abstract

Over a period of five years, antemortem diagnosis of leptomeningeal spread was made in six of thirteen children with high grade astrocytomas. These included four of seven children with hemispheral tumors and two of six children with malignant brainstem gliomas. Leptomeningeal spread was diagnosed by the clinical picture and CSF profile. Meningeal spread occurred an average of 5 months (range 0–16) after initial diagnosis of tumor was made. Several patients responded well to local radiation and/or chemotherapy. Mean survival after evidence of meningeal spread was 7 months (range 2–16) with one patient still alive.

Meningeal spread of malignant childhood astrocytomas appears to be common and should be sought for in these patients as local radiation is beneficial. Serious consideration should be given to a controlled trial of prophylactic craniospinal radiation in thee tumors. The role of chemotherapy also requires further study.

Introduction

Glioblastoma multiforme is a malignant brain tumor of glial origin with rapid growth and a fatal course. The tumor comprises approximately 15–20% of intracranial tumors in adults 3–11% in children (1). Its course is characterized by rapid local extension, sometimes with meningeal involvement, but it only occasionally metastasizes via cerebrospinal-fluid (CSF) pathways. This report describes our experience with six children with malignant astrocytomas (grades III and IV) in whom spinal meningeal dissemination was diagnosed. Our data suggest that CSF metastases may be a common complication of high grade astrocytomas, and that the use of spinal irradiation or chemotherapeutic agents is of short-term benefit.

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Materials and methods

During the five year period, June 1977 to June 1982, 90 new cases of primary brain or optic nerve tumors were diagnosed in children under the age of 17 years at the Johns Hopkins Hospital pediatric neurology service. Of this group, 19 had supratentorial astrocytomas of which seven were grade III or IV based on the pathologic criteria defined by Kernohan and Sayre (2). All 19 were biopsied. Ten had brainstem gliomas of which 4 had a clinical picture and course consistent with a low grade glioma (1 confirmed by biopsy) and 6 appeared to have a grade III–IV glioma of which 3 were confirmed by biopsy or CSF cytopathology (3).

At many institutions, it is now common to restrict the term glioblastoma multiforme to either grade IV astrocytomas or poorly differentiated anaplastic tumors of glial origin for which there is no definite evidence of a preexisting astrocytoma.

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Grade III astrocytomas are often referred to as malignant or anaplastic astrocytomas. Since it is difficult to clearly distinguish between grades three and four astrocytomas on the basis of a biopsy specimen (4), these cases have been combined and represent the study population. Autopsy permission was denied.

Results

Among the thirteen children with high-grade tumors, six had clinical evidence of meningeal spread (Tables 1 and 2, Cases 1–6). There were no known instances of meningeal spread in the twelve children with grade I and II supratentorial astrocytomas or the four children with low-grade brainstem gliomas.

Of the six cases with evidence of meningeal spread, four had primary hemispheral tumors and two had pontine gliomas. The mean age of onset was 9.1 years for the hemispheral tumors (range: 5 months–15 years) and 6.9 years for the brainstem gliomas (range: 4 9/12–9 years). Diagnoses were based on neuroradiographic studies in all cases and, in 5 of the cases, on tumor biopsy as well. Diagnosis in case 5 (not biopsied) was based on the clinical picture, CT scan and malignant tumor cells in CSF (Fig. 1A). Meningeal spread of the primary tumor in Cases 1–6 was diagnosed by clinical symptomatology, neurological exam, CSF cytology (Fig. 1B) and response to therapy. All but Case 5 had alterations in tone and most had diminution of reflexes. In the five cases (2–6) where a lumbar puncture or shunt tap was performed, all had abnormal CSF findings (Table 3): cytopathology positive in 3/5, increased protein 3/5, leukocytes 3/5. In patients 2 and 3, cranial computerized tomography showed abnormal tentorial or periventricular enhancement, suggestive of CSF spread (Fig. 2).

The mean interval between diagnosis of the primary tumor and evidence of meningeal involvement was five months (range 0–16 months). Following the diagnosis of spinal metastasis, all patients except Case 4 received either local cord irradiation, intrathecal methotrexate/thiotepa or systemic cisplatinum. Symptomatic response was noted in every case, ranging from diminution of pain to improved mobility. In the five deceased patients in whom antemortem diagnosis of meningeal spread was made, mean survival was 13 months from the diagnosis of the primary tumor (range: 3–22 months) and 7 months from onset of myelopathy or radiculopathy (range: 2–16 months). One patient (Case 5) is still alive 14 months from the diagnosis of her tumor and of CSF spread.

Table 1. Clinical summary of patients.

Case	Age at time of diagnosis (years)	Presenting symptoms	Location of tumors	Pathology	Initial treatment	Survival after diagnosis (months)
1	10	Gait disorder	R parietal	Grade IV	4500 rads whole brain together with metronidazole 5400 rads to tumor	22
2	15	Headache & seizure	L temporo-parietal	Grade IV (gemistocytic)	3000 rads whole brain	3
3	11	Seizures & lethargy	L temporo-parietal	Grade III	4500 rads whole brain 5940 rads to tumor	15
4	5/12	Lethargy & decreased feeding	L temporo-parietal	Grade IV	3960 rads to tumor	16
5	9	Headaches & cranial nerve palsies	Brainstem	Malignant astrocytes on cytopathology of CSF	4500 rads whole brain 5400 rads posterior fossa	Alive at 14 mo
6	4 9/12	Right cerebellopontine angle hemorrhage	Brainstem	grade III	5040 rads posterior fossa	7

Table 2. Clinical course of meningeal spread of patients with antemortem diagnosis.

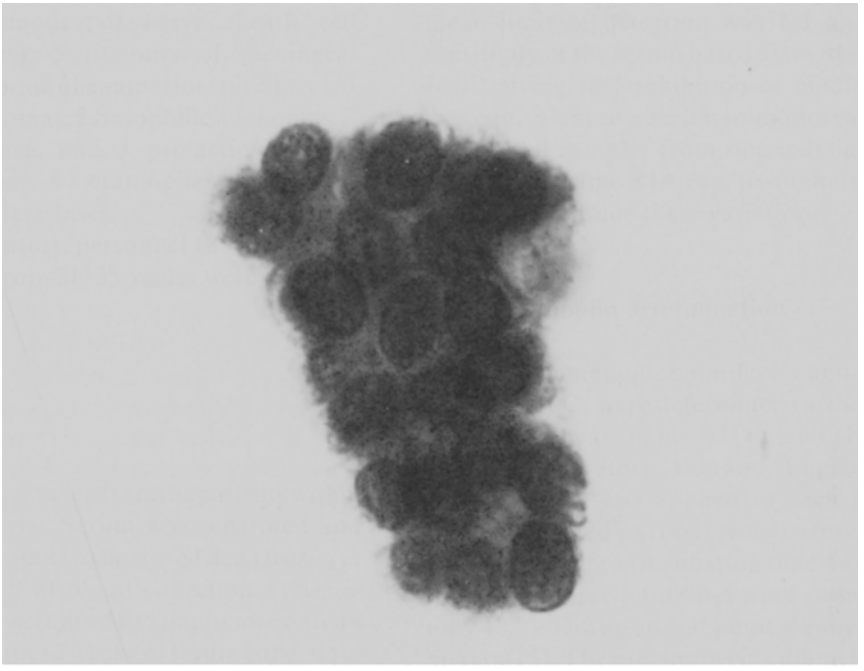
Case	Time from diagnosis tumor to meningeal spread (months)	Clinical symptoms	Status of primary tumor at time of meningeal spread	Treatment	Initial response to therapy	Survival after meningeal spread (months)
1	16	Radiating lumbosacral pain, decreased sensation over T10-T12 distribution and diminished left knee jerk	Recurrence two months prior to meningeal spread	1200 rads to thoracolumbar spine	Complete	6
2	1	Nuchal rigidity, bilateral arm weakness, back pain and constipation	Enlarging, unresponsive to therapy	2000 rads to cervical spine	Partial	2
3	8	Low back pain	Smaller by CT scans, no clinical symptoms referrable to brain	Cis-platinum	Complete	7
4	0	Areflexia in lower extremities	Primary tumor and meningeal spread diagnosed concurrently	None		16
5	0	(Positive cytopathology on shunt tap)	Primary tumor (swollen pons by CT scans) and meningeal spread diagnosed concurrently	Received 3500 rads spinal radiation prophylactically	-	Alive at 14 months
6	5	Abrupt onset of flaccid paraparesis, urinary retention, and lax anal sphincter tone. Normal arm function.	Progressively enlarging	Steroids and 2100 rads to lumbosacral spine	Partial	2

Discussion

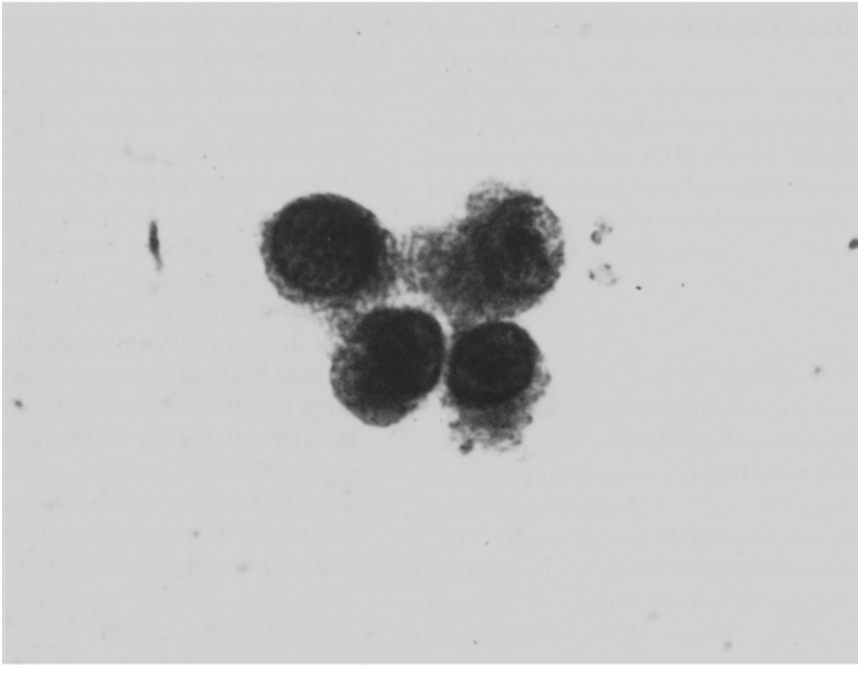
Subarachnoid dissemination of malignant astrocytoma/glioblastoma multiforme, outside the area of the primary tumor or operative site, was previously considered quite rare (5, 6). Recently, however, two large autopsy series of 77 patients with high grade astrocytomas, reported an approximately 25% incidence of leptomeningeal metastases in patients ranging from 5 to 69 years, two of whom

Table 3. CSF profile in patients with antemortem diagnosis of meningeal dissemination.

Case	Source (mg/dl)	Glucose (mg/dl)	Protein	WBC	RBC	Cytopathology
1	-	-	-	-	-	-
2	LP	8	234	102	7600	Positive
3	LP	42	2610	88	2500	Necrotic debris
4	LP	38	37	1	0	Positive
5	Shunt tap	72	5	0	0	Positive
6	LP	92	77	26	628	Negative $\times 2$



(A)



(B)

Fig. 1 CSF Cytopathology in malignant astrocytomas. (A) Tissue fragment of tumor cells in the CSF in malignant brainstem glioma. Note the pleomorphism. Millipore filter × 787. (B) Group of tumor cells in CSF of patient with hemispheric malignant astrocytoma. Note the nuclear membrane thickness irregularity and prominent nucleoli. Millipore filter × 787.

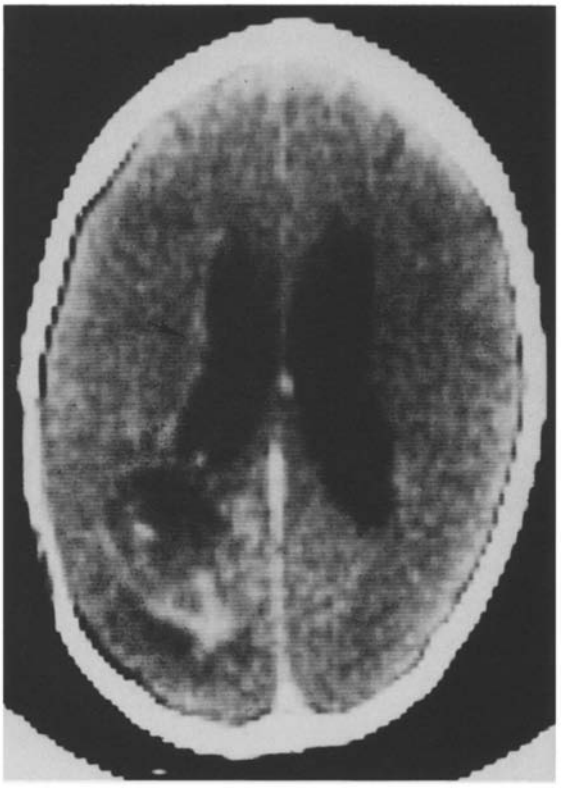


Fig. 2. CT evidence of CSF spread. Enhanced CT scan of the patient with left temporoparietal grade III glioma and clinical evidence of cerebrospinal dissemination. Note periventricular enhancement on left side suggesting CSF spread (arrow).

were children (7, 8). In one of these series (8) eight of twelve cases were diagnosed antemortem. A small group of five patients with atypical juvenile astrocytomas and subarachnoid spread has also been reported (9). Spinal leptomeningeal metastases originating from a pineal glioblastoma multiforme have also been reported (10). The frequency of subarachnoid spread of malignant brainstem gliomas remains controversial. One recent pediatric autopsy series reported anatomical evidence of spread in seven of sixteen cases (11) while another series with pediatric and adult cases found only one instance of subarachnoid spread in 25 cases (12). Finally, in a series with fifteen cases presenting as brainstem gliomas (13), five (33%) developed leptomeningeal metastases.

This study differs from previous reports in that it is restricted to the pediatric population, specifically children less than age 17. In our 5 year period of analysis none of the twelve patients with grade one or two supratentorial astrocytomas nor the four patients with low-grade brainstam gliomas showed clinical evidence of subarachnoid spread. However, six out of thirteen cases of malignant astrocytomas (grades three or four) developed signs or symptoms of spinal meningeal seeding.

For the last three years of the study, evidence of meningeal spread was systematically looked for in all patients with high grade gliomas. In our patients, there was no specific clinical pattern characteristic of leptomeningeal invasion. Findings included: stiff neck, back pain, sensory loss, hypotonia, weakness, depressed or absent reflexes and decreased anal tone or bowel and bladder incontinence. These are similar to those described in adults with meningeal spread and to adults with carcinomatous meningitis (8). Although it was sometimes difficult to determine whether these clinical findings represented meningeal spread or direct tumor extension, particularly in the case of brain stem gliomas, supportive evidence included the presence of nuchal rigidity, the CSF profile, or CT scans. As meningeal irritation may also be the result of cerebellar herniation, subarachnoid, hemorrhage, infectious meningitis or spillage of necrotic tumor material producing a chemical meningitis (14), the analysis of CSF and cranial CT scans was helpful, especially when other findings consistent with a gliomatous meningitis were present. Cranial CT scans demonstrated periventricular enhancement in two patients, findings supportive of a disseminated meningeal tumor. The utility of cranial CT scans in providing reliable evidence for meningeal invasion has been described (15). Finally, the beneficial response of spinal cord signs and symptoms to local irradiation or chemotherapy has further supported the diagnosis of spinal subarachnoid spread.

The current prognosis of patients with glioblastoma multiforme is poor (16). It has been suggested that the documentation of spinal spread is not worthwhile since the primary tumor is fatal before symptoms of spinal seeding are present (17). In our cohort, spinal cord symptoms were the source of great discomfort and occurred months prior to death in all our cases. Significant, albeit temporary, improvements in the well-being of the patients were achieved with therapy. As newer primary che-

motherapeutic agents providing further increases in survival time are discovered, recognition of subarachnoid spread will become increasingly important.

Some authorities now recommend prophylactic craniospinal irradiation for all childhood malignant cerebellar astrocytomas (18) or at least for selected infratentorial malignant astrocytomas (19). In one recent series of thirteen children with cerebellar malignant astrocytomas, five of six who received only cranial irradiation developed subarachnoid metastases while none of the seven who received craniospinal irradiation demonstrated subarachnoid spread (18). However, all of those who developed subarachnoid spread had received less than 5 000 rads to the primary tumor while those who did not had received 5 550–5 580 rads to the primary site raising the issue of whether the initial dose of radiation is the determining factor (20). Care must also be taken in differentiating subarachnoid spread defined by clinical symptomatology versus asymptomatic positive cytopathology (21).

We report a 46% incidence of subarachnoid spread in malignant childhood astrocytomas with a good temporary response to palliative therapy in the majority of patients. It is not clear when the spread occurs. If it occurs at the time of biopsy or initial tumor occurrence, as has been reported in germinomas, then prophylactic spinal irradiation is warranted. On the other hand, if subarachnoid spread occurs at the time of tumor recurrence or later, then prophylactic spinal radiation would be ineffective and contraindicated. A controlled trial of prophylactic spinal radiation versus radiation at the time of tumor spread merits consideration. Chemotherapy of brain tumors in general is still in its infancy. A continuous search for more effective chemotherapy is essential.

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