Primary cerebellar glioblastomas multiforme in children

Report of four cases

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Primary cerebellar glioblastomas multiforme are exceedingly rare in children. The authors therefore retrospectively characterized the clinical behavior and pathological features of these tumors. A review of the database at the Hospital for Sick Children, Toronto, Canada revealed four patients with cerebellar tumors that displayed significant pleomorphism, hypercellularity, mitoses, and necrosis with pseudopalisading. The authors performed a detailed clinical, radiological, histological, and immunohistochemical analysis of the tumors in these four children (three boys and one girl; average age at presentation 7 years; range 21 months–15 years). Magnetic resonance imaging and computerized tomography most commonly revealed a large lesion with minimal edema, inhomogeneous contrast enhancement, and a discrete border. Tumor resection was subtotal in one patient and gross total in three patients. Immunostaining of the tumor cells with antisera to glial fibrillary acidic protein and vimentin was positive in varying degrees. Initial adjuvant therapy consisted of local radiation only (one patient), chemotherapy only (one patient), and radiation and chemotherapy (one patient). One patient received no adjuvant therapy. Tumor recurrence was documented in all patients: two local recurrences (at 3.5 and 7 months), one spinal recurrence (at 14 months), and one local recurrence with ventricular and spinal spread (at 8 months). Ultimately, three of the four patients developed leptomeningeal tumor spread. Patient follow up ranged from 8 to 17 months (mean 12.5 months). Three patients were dead at last follow up with a mean survival of 15 months.

The prognosis for patients with cerebellar glioblastomas is extremely poor, and the tumor has a tendency for cerebrospinal fluid dissemination. The optimal management of patients harboring of these difficult-to-treat tumors, including the role of craniospinal radiation and chemotherapy, has not yet been achieved.

Key Words • cerebellum • pediatric tumor • glioblastoma multiforme

Astrocytomas

Astrocytomas of the cerebellum are relatively common tumors in children, and the vast majority are of benign histological composition. Glioblastomas multiforme (GBMs) of the cerebellum (World Health Organization [WHO] Grade 4 astrocytoma) are exceedingly rare in children, with only occasional isolated reports. We present our experience at the Hospital for Sick Children, Toronto, Canada, involving four children with cerebellar GBMs. We performed a detailed clinical, pathological and radiological analysis to better characterize these tumors. Hoping to shed light on the mode of failure of current treatment protocols, we paid more attention to the method of tumor progression and recurrence.

Patient and Clinical Data

A review of the clinical database at the Division of Neurosurgery at the Hospital for Sick Children in Toronto, Canada since 1955 revealed seven patients in whom a primary malignant cerebellar astrocytoma had been diagnosed. Brainstem tumors were excluded. Only patients with tumors that had features of significant pleomorphism, hypercellularity, mitoses, and necrosis with pseudopalisading were included, leaving four cases that met the WHO criteria of Grade 4 astrocytoma (GBM). The clinical records, imaging studies, and pathological specimens obtained in these four patients were then reviewed in detail.

Of the four children, there were three boys and one girl, who at presentation ranged in age from 21 months to 15 years (mean 7 years). Their presenting symptoms included headache, nausea and vomiting, ataxia, and neck pain. The mean duration from onset of first symptoms to presentation was 4.6 weeks. On examination, three children were noted to have objective cerebellar findings (nystagmus and/or ataxia). Two children had papilledema.

Neuroradiological Findings

Magnetic resonance (MR) imaging was available in three patients and computerized tomography (CT) only in one additional patient. These data are summarized in Table 1. All tumors exhibited a discrete border, enhanced...
inhomogeneously with contrast administration, and had either absent or only moderate associated edema. In Case 4, a center of T<sub>1</sub>-weighted hyperintensity within a hypointense tumor suggested the possibility of a small intratumoral hemorrhage. There was no definite evidence of intracranial spread on any of these preoperative images. Two tumors appeared to invade the fourth ventricle, and one extended into the foramen magnum. The brainstem was not involved in any case, other than involvement of the middle cerebellar peduncle in Case 2. In the three cases in which CT scans were available, the precontrast CT revealed tumors that varied from iso- to slightly hyperdense relative to brain, in addition to hypodense cystic areas. Of interest, we noted that one patient (Case 4) had a normal CT scan just 2 months prior to diagnosis of a 42-mm cerebellar GBM on MR imaging (Fig. 1 left). When this child did develop recurrent tumor, it did not display any significant gadolinium enhancement (Fig. 1 right).

**Operations and Postoperative Courses**

All four children underwent resective surgery, which was subtotal in one and gross total in three. There were no intraoperative complications. The tumor was most commonly described as being soft, jellylike, and dark purple in color.

The single postoperative complication occurred in a 15-year-old boy (Case 2 from Table 2) who developed a posterior fossa epidural hematoma that required urgent evacuation and ventriculoperitoneal shunt placement on postoperative Day 2. He recovered well but was left with a mild hemiparesis. He was the only child to require permanent placement of a cerebrospinal fluid (CSF) shunt.

Adjuvant therapy consisted of local radiation only in one case (5200 rad), chemotherapy only in one case (cyclophosphamide and vincristine), and combined radiation and chemotherapy in one case (5000 rad and “8-in-1” multiple agent chemotherapy regimen) (Table 2). In all cases radiation consisted of a local dose to the posterior fossa only. No elective craniospinal radiation was given. One young boy (age 21 months) received no adjuvant therapy initially.

Patient follow up ranged from 8 to 17 months (mean 13.3 months). There were three deaths (all due to tumor recurrence), occurring at 13 months, 15 months, and 17 months. Tumor recurrence was radiologically documented in all four children (Table 3 and Fig. 1 right). In three patients tumor recurrence occurred locally in the posterior

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### TABLE 1

Radiological characteristics of four pediatric patients with primary cerebellar GBM

<table>
<thead>
<tr>
<th>Case No.</th>
<th>CT/ MR</th>
<th>Max Diameter (mm)</th>
<th>Location</th>
<th>T&lt;sub&gt;1&lt;/sub&gt;</th>
<th>T&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Cystic Portion</th>
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<td>—</td>
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<td>moderate</td>
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<td>midline</td>
<td>hypo/ hyper</td>
<td>hyper</td>
<td>no</td>
<td>minimal</td>
</tr>
</tbody>
</table>

* All tumors enhanced inhomogeneously and had discrete borders. Abbreviations: hypo = hypointense; hyper = hyperintense; T<sub>1</sub> = T<sub>1</sub>-weighted; T<sub>2</sub> = T<sub>2</sub>-weighted; — = not available.

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Fig. 1. Case 4. **Left:** Axial T<sub>1</sub>-weighted MR image, after gadolinium enhancement, demonstrating a large, inhomogeneously enhancing tumor with mixed signal intensity centrally, suggestive of possible intratumoral hemorrhage. This image was obtained only 2 months after a normal plain CT scan. **Right:** Axial T<sub>1</sub>-weighted MR image, after gadolinium enhancement, obtained at tumor recurrence 7 months after gross-total resection and chemotherapy. This image demonstrates a large local recurrence without contrast enhancement.
fossa (one with concurrent intraventricular and spinal metastases), and in one patient spinal metastases occurred without evidence of cerebellar progression (this patient had undergone a subtotal resection of his cerebellar tumor, followed by local radiation and chemotherapy). Treatment of local recurrence included reoperation and chemotherapy in Case 1 (the patient died 13 months after initial presentation) and medical palliation in Case 4 (the patient is currently alive at 8 months follow up). In Case 2, the patient experienced spinal recurrence and was treated with 5000 rad of spinal radiation therapy (the patient died at 15 months follow up, 1 month after recurrence). In Case 3, the patient experienced local recurrence with intraventricular and spinal dissemination and was treated with chemotherapy (“8-in-1” multiple agent regimen). She died at 17 months follow up (9 months after the onset of recurrence).

### Pathological Findings

A summary of the pathological findings is presented in Table 4. All tumors met the WHO histological criteria of Grade 4 astrocytoma. All tumors displayed hypercellularity, pleomorphism, mitoses, and necrosis with pseudopalisading. Endothelial proliferation was seen in three cases.

A quantitative analysis of MIB-1 positivity index was performed and recorded as a percentage of nuclei with positive staining. The immunostaining positivity of tumor cells to glial fibrillary acidic protein (GFAP) and vimentin was graded as 0 (no tumor cells positive), 1+ (few tumor cells positive), 2+ (many tumor cells positive), or 3+ (most tumor cells positive). Quantitative MIB-1 analysis ranged from 32 to 73% nuclear immunopositivity. In three tumors it was possible to see the margin between the tumor and normal brain, and in all such cases the tumor was infiltrative. In no case could evidence of subarachnoid space invasion be seen microscopically. There was no evidence of hemosiderin, calcification, or lymphocytes in any of the specimens. Individual cell necrosis, to be distinguished from confluent necrosis, was present in every case.

Most tumors (Cases 1, 3, and 4) displayed only minimal staining with GFAP. In all tumors, staining was minimally to moderately positive for vimentin, a more primitive intermediate filament.

Electron microscopy was performed on the tumor specimens from Cases 1 and 4 and revealed cell processes in intermediatemediate filament. In Case 1, cytoplasmic intermediate filaments and revealed cell processes in intermediate filament. In Case 1, cytoplasmic intermediate filaments and revealed cell processes in intermediate filament. In Case 1, cytoplasmic intermediate filaments and revealed cell processes in intermediate filament. In Case 1, cytoplasmic intermediate filaments and revealed cell processes in intermediate filament. In Case 1, cytoplasmic intermediate filaments.

### Discussion

**Clinical Factors**

Primary cerebellar GBM is a very rare tumor, especially in children. Malignant tumors account for less than 5% of all pediatric cerebellar astrocytomas.\(^2\) Even in a series of the relatively rare intracranial pediatric GBMs, only 5% of these were cerebellar in location.\(^4\)

The rapidity of the onset of symptoms in these tumors is striking, with a mean duration of 4 to 5 weeks prior to presentation.\(^17\) Most commonly this consisted of headache, nausea, vomiting, and ataxia. In low-grade cerebellar astrocytomas the onset of symptoms is characteristically chronic and insidious, with a mean duration of 3 to 5 months.\(^1,2,16\)

Unfortunately, the poor prognosis for patients with this condition has been well established in previous publications. A review of well-documented cases of pediatric cerebellar malignant astrocytomas reveals a total of 14 patients with Grade 4 GBMs; 11 of these patients died with a mean survival time of 9.9 months. Three of these patients were alive with a mean follow up of 24 months.\(^3,6,10,13-15,17,18\) The prognosis appears very minimally better for patients with Grade 3 malignant astrocytomas: there are 12 such documented pediatric cerebellar cases with six deaths (mean survival time of 11.9 months) and six patients alive with a mean follow up of 42 months.\(^3,7,10,15,18\) In our series, three patients died with a...
mean survival of 15 months and one was alive at last follow-up with recurrent disease. However, the prognosis for pediatric patients does appear marginally better than for adults with cerebellar GBMs, with a reported 3-month mean survival time.12

Although there are few data to support significant benefit from surgery, it would seem reasonable to attempt a gross-total resection in all feasible cases of cerebellar GBM. However, the dilemma that presents most often is whether there is any value in performing a second operation for recurrent disease. In our series three children had local recurrence and only one underwent reoperation. This patient, Case 1, experienced recurrence at 3.5 months and then survived another 9 months after reoperation. However, this case was unique in that the patient had not received any adjuvant therapy after the initial operation and, therefore, this was treated as a “new” case in which radiation and chemotherapy followed the reoperation. Fresh, et al.,5 reported on a case in which a patient with cerebellar GBM underwent reoperation twice, at 17 months and 21 months after the initial surgery, and survived a total of 26 months. However, when contemplating reoperation, thought should be given to the time to recurrence, the patient’s initial response to therapy, and, perhaps, special consideration for the patient who was too young initially to receive radiation therapy, thereby using a second operation as a prelude to radiation.

The need for postoperative radiation of at least the posterior fossa in children older than 3 years of age is not in question. In the few cases of patients treated without radiation, none survived longer than 1 month.10 The two children in our series who were too young to receive radiation developed tumor recurrence at 3.5 and 7 months, compared with 8 and 14 months for the two children who did receive radiation. However, much of the controversy in the management of these tumors has revolved around the need for elective craniospinal irradiation. Salazar15 had stressed the high incidence of CSF dissemination of cerebellar GBMs in patients who did not receive craniospinal irradiation (five of six patients) and the virtual elimination of this complication with elective neuraxis radiation (none of seven patients). In contrast, Kopelson16 did not document any leptomeningeal metastases in a series of eight patients and believed that primary tumor control with a generous dosing of posterior fossa radiation was the most effective means of reducing CSF dissemination. Another explanation for the apparent differences in tendency for CSF spread between these two series is that Salazar reported on 13 children, whereas Kopelson’s series consisted of six adults and only two children. In fact, the only reports of CSF dissemination of cerebellar GBMs have been of series consisting exclusively or predominantly of children.2,3,14,15,17 Authors of these series reported rates of leptomeningeal spread ranging from 17 to 66%. Our exclusively pediatric series also suggests a propensity for these tumors to spread via CSF pathways, which is a behavior mimicking that of medulloblastoma. None of our patients received elective craniospinal radiation and three patients developed CSF dissemination. Therefore, it is possible that the natural behavior and, therefore, the mode of failure of therapy, of cerebellar GBM differs between adults and children. This might suggest a modified craniospinal radiation approach to these tumors in the pediatric population that is similar to the established treatment of medulloblastoma. Admittedly, one could still argue that all our cases of CSF spread also represent lack of local disease control; two patients had concomitant cerebellar recurrence and the other had only a subtotal resection of his cerebellar tumor. However, given the very poor survival time we have been able to offer these children with our current radiation protocols, perhaps a different approach that focuses on this established mode of tumor spread might be appropriate.

The role of chemotherapy in cerebellar GBMs has not been well studied. Again, our series is too small for us to decide if chemotherapy did provide any significant survival time benefit, but clearly, it offers the only reasonable treatment available to very young children in whom the effects of brain radiation would be devastating. Beyond this, the role of chemotherapy is not established and is open to clinical trials.

Radiological Factors

The MR and CT imaging revealed that all tumors were very large at presentation, each greater than 40 mm in maximum diameter. The rapid growth potential of these lesions is shown in Case 4 in which a CT scan was entirely normal 2 months prior to the discovery of a 42-mm midline cerebellar tumor (Fig. 1). Although the presence of inhomogeneous contrast enhancement and a cystic component with ring enhancement may be expected from a highly malignant tumor, it was surprising to find relatively little edema and an invariably discrete border with normal brain. These characteristics have been noted previously and, although potentially helpful to distinguish the tumor from the common cerebellar metastasis of the adult, they do not provide specific features to help distinguish it from other common pediatric cerebellar tumors.8,11 The precontrast CT density was varied from iso- to hyperdense and was not characteristic.

Pathological Factors

According to the WHO criteria, the diagnosis of a Grade 4 astrocytoma requires the presence of confluent necrosis, usually with pseudopalisading, or prominent endothelial proliferation.7 In this study, all tumors exhibited necrosis with pseudopalisading. In addition, three cases displayed evidence of endothelial proliferation.

Our thorough study of the immunophenotype of cerebellar GBMs revealed that immunostaining with GFAP was variable, ranging from diffuse to patchy and isolated positivity. This is not unusual for very high grade astrocytomas.9 However, in all cases positive staining was demonstrated in at least some tumor cells. Vimentin, generally considered a more primitive intermediate filament, also stained positive in all cases. This may reflect the poorly differentiated nature of these tumors.

Conclusions

Cerebellar GBM in children is a highly malignant tumor that presents rapidly as a large posterior fossa mass. The pathological diagnosis is based on characteristics common to GBMs in other locations, but the tumor may have variable immunopositivity to GFAP and vimentin.
Patient survival time is generally less than 18 months, with a propensity for CSF dissemination during the course of disease. Current treatment protocols have very limited success and new modes of therapy, including the use of craniospinal irradiation and chemotherapy, need to be investigated.

References


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