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Pediatric primary intramedullary spinal cord glioblastoma

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Abstract

Spinal cord tumors in pediatric patients are rare, representing less than 1% of all central nervous system tumors. Two cases of pediatric primary intramedullary spinal cord glioblastoma at ages 14 and 8 years are reported. Both patients presented with rapid onset paraparesis and quadraparesis. Magnetic resonance imaging in both showed heterogeneously enhancing solitary mass lesions localized to lower cervical and upper thoracic spinal cord parenchyma. Histopathologic diagnosis was glioblastoma. Case #1 had a small cell component (primitive neuroectodermal tumor-like areas), higher Ki67, and p53 labeling indices, and a relatively stable karyotype with only minimal single copy losses involving regions: Chr8:pter-30480019, Chr16:pter-29754532, Chr16:5616245-88668979, and Chr19:3284902-pter on retrospective comparative genomic hybridization using formalin-fixed, paraffin-embedded samples. Case #2 had relatively bland histomorphology and negligible p53 immunoreactivity. Both underwent multimodal therapy including gross total resection, postoperative radiation and chemotherapy. However, there was no significant improvement in neurological deficits, and overall survival in both cases was 14 months. This report highlights the broad histological spectrum and poor overall survival despite multimodality therapy. The finding of relatively unique genotypic abnormalities resembling pediatric embryonal tumors in one case may highlight the value of genome-wide profiling in development of effective therapy. The differences in management with intracranial and low-grade spinal cord gliomas and current management issues are discussed.

Introduction

Spinal cord tumors are rare in children, representing less than 1% of all central nervous system (CNS) tumors. Within this small fraction, intramedullary spinal cord (ISC) tumors constitute about 35% of the spinal tumors found in children compared to 5% in adults. Low-grade gliomas such as ependymomas and astrocytomas account for the majority, with only about 1-3% being high-grade gliomas. A recent review of the cases of pediatric ISC-glioblastoma (GBM) reported in the last two decades is summarized in Table 1. Patients were treated with multimodality therapeutic regimens similar to their adult counterparts. The roles of maximum safe surgical resection and radiotherapy are well established in the treatment of pediatric high-grade glioma in the intracranial location, and in non-infiltrative spinal cord tumors, but not in high-grade spinal cord gliomas where recent studies discourage the use of radical surgery. The role of chemotherapy remains undefined. Based on this limited dataset, critical underlying genomic events and the determination of the optimal therapeutic approach in this rare disease are unknown. This report describes two cases of pediatric primary ISC-GBM. Both had gross total resection, and were treated with adjunctive chemotherapy and radiation therapy as per the Children’s Oncology Group protocol ACNS0126 for intracranial gliomas extrapolated to high-grade spinal cord gliomas. Results of comparative genomic hybridization in one case in whom adequate tissue and call rate was available is also provided. A review of pertinent literature aims to provide a comparative and balanced perspective.

Case #1

A 14-year-old Asian–American female presented with a six-month history of lower extremity dysesthesias, which progressed to lower extremity weakness and gait difficulties several days before presentation. Magnetic resonance imaging (MRI) of the brain and spine performed at an outside hospital (images currently unavailable) revealed an intramedullary enhancing mass extending from the level of the sixth cervical (C6) to fifth thoracic (T5) vertebra. She underwent cervical and thoracic laminectomies with gross total resection of the tumor. The histopathologic diagnosis was GBM (Figure 1A–E). Postoperatively, the patient had paraplegia and an upper extremity strength of 1/5, which improved to 4/5 within two weeks with steroids and physical therapy. During rehabilitation, she required treatment for wound infection and dehiscence. She began the Children’s Oncology Group protocol ACNS0126 with radiation therapy and chemotherapy in the treatment of high-grade glioma. She received 5040 cGy to her cervical and thoracic spine in 28 evenly divided fractions. On the fifth day of radiation therapy, she began oral temozolomide at 90 mg/m2/day for six weeks, followed by a four-week rest. Maintenance therapy consisted of 10 courses of 28-day cycles of oral temozolomide 200 mg/m2/day for five days, followed by 23 days of rest. During this therapy, she reported subjective improvement in leg strength, but remained wheelchair-bound.

MRI of the spine six months after resection showed progression of the tumor, extending from the level of C5 to T3. Post-radiotherapy changes were seen throughout the spinal axis. Nine months after resection, MRI of the spine showed a stable lesion, with cord expansion and myelomalacia in a similar distribution. Whole-body PET imaging from the skull to the thigh was negative for metastasis or lymphadenopathy. Fourteen months after resection, the patient died while in hospice care.

Case #2

An eight-year-old African American female presented with a three-week history of neck pain and weakness, which progressed to significant weakness in all extremities. MRI of the brain and spine revealed an intramedullary enhancing mass originating from the central portion of the spinal cord, extending from the level of C3 to T4 with significant cord expansion from C3 to T3 (Figure 2A–E). Of note, pre-
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Immunostain for epidermal growth factor receptor (EGFR) was negative. The ultrastructural evaluation in case #1 revealed pleomorphic cells with short bulbous projections and a paucity of organelles except for mitochondria. The nuclei were pleomorphic with conspicuous heterochromatin. Glial filaments in every cell were scattered throughout the cytosol in discreet bundles, often associated with Rosenthal bodies. Microtubules were found in close-packed bundles or loose arrays in the cytosol and cellular projections. Tumor samples from case #1, were previously analyzed using array comparative genomic hybridization (aCGH). These analyses revealed a relatively stable karyotype with only minimal single copy losses involving regions: Chr8:pter-30480019, Chr16:pter-29754532, Chr16:56160245-88668979, and Chr19:32848902-pter.

Pathology

Histological examination of the resected masses in both cases revealed high-grade infiltrating astrocytic neoplasms with necrosis and microvascular proliferation. No obvious pseudopalisading around the areas of necrosis were seen in either case. Individual neoplastic cells demonstrated significant nuclear pleomorphism, anaplasia and high mitotic activity with scattered apoptotic bodies (Figures 1A and B; 2F-J, respectively), including small cells focally resembling a primitive neuroectodermal tumor (PNET) but with microvascular proliferation (Figure 1B). A diagnosis of GBM, WHO grade IV, was rendered. Diffuse immunopositivity for glial fibrillary acidic protein (GFAP) supported the diagnoses in both cases (Figures 1C and 2K).

In case #1, there was a small cell component and more conspicuous anaplasia as compared to case #2. The neoplastic cells in case #1 showed a high Ki67 (MIB1) immunohistochemical nuclear labeling index of up to about 30%, but a rather low p53 labeling index of less than 5% (Figure 2L and M, respectively). Immunostain for epidermal growth factor receptor (EGFR) was negative. The ultrastructural evaluation in case #1 revealed pleomorphic cells with short bulbous projections and a paucity of organelles except for mitochondria. The nuclei were pleomorphic with conspicuous heterochromatin. Glial filaments in every cell were scattered throughout the cytosol in discreet bundles, often associated with Rosenthal bodies. Microtubules were found in close-packed bundles or loose arrays in the cytosol and cellular projections. Tumor samples from case #1, were previously analyzed using array comparative genomic hybridization (aCGH). These analyses revealed a relatively stable karyotype with only minimal single copy losses involving regions: Chr8:pter-30480019, Chr16:pter-29754532, Chr16:56160245-88668979, and Chr19:32848902-pter. None of the frequent losses, gains, and amplifications seen in adult GBM were identified in this sample (see Discussion).

In case #2, the neoplastic cells were relatively bland as compared to case #1. High-grade cytological features were not apparent on frozen sections, but diagnostic features were seen on FFPE sections. The neoplastic cells showed a high Ki67 (MIB1) immunohistochemical nuclear labeling index of up to about 30% (Ki67 stain; 200X). The tumor shows a high Ki67 (MIB1) immunohistochemical nuclear labeling index of up to about 70% (p53 stain; 200X).

Figure 1. Case #1. (A) Densely cellular neoplasm, with hyperchromatic and pleomorphic astrocytic cells in a well-formed fibrillary background meshwork, with focal necrosis (H&E stain; 100X magnification). (B) Densely cellular infiltrating portion of the neoplasm, with markedly hyperchromatic and pleomorphic overlapping astrocytic cells in a rather sparse fibrillary background with focal necrosis, including small cells focally resembling a primitive neuroectodermal tumor but with microvascular proliferation (H&E stain; 200X). (C) The tumor shows diffuse glial fibrillary acidic protein (GFAP) positivity with dense fibrillary network in portions (GFAP stain; 400X). (D) The tumor shows a high Ki67 (MIB1) immunohistochemical nuclear labeling index of up to about 70% (p53 stain; 200X).
Discussion

The ISC is the location of only one third of 1% of pediatric CNS tumors. Of these, high-grade gliomas such as the two ISC-GBM cases reported here constitute only about 1-3%, far outnumbered by the low-grade gliomas and ependymomas. These are rare tumors, and even with many recent advances in preoperative imaging, micro-neurosurgery and radiation/chemotherapy protocols, the overall survival after multimodality therapy has been comparable to that in adults. A review of cases of pediatric ISC-GBM reported in the last two decades is summarized in Table 1.

Clinical features

The clinical presentation of any ISC tumor relates to the region of the spinal cord involved. Up to 60% of pediatric ISC astrocytomas can show holocord presentation, which is unusual in adults. The most common symptoms in pediatric ISC tumors are pain (42%), motor regression (36%), gait abnormalities (27%), torticollis (27%), and progressive kyphoscoliosis (24%). The cases reported here presented with non-specific neck pain or lower extremity dysesthesias, which soon worsened to progressive weakness and gait difficulties. In a recent study, preoperative symptom duration of more than 180 days was associated with improved survival in infiltrative spinal cord astrocytomas.

Radiological features

Most cases of ISC-GBM showed MRI imaging characteristics similar to intracranial GBM. Occasional atypical features included an
Figure 2. Case #2. (A) T1 weighted sagittal magnetic resonance images without contrast show an intramedullary hypointense mass lesion present within the central portion of the cervical spinal cord from C3 to T3 levels, producing expansion. (B) T1 weighted sagittal MR images with contrast show an intramedullary enhancing mass lesion present within the central portion of the cervical spinal cord, originating from the region of the central canal, producing expansion. The spinal cord measures 13 mm at the greatest AP diameter. The mass shows rim enhancement with central cystic changes and is surrounded by normal-appearing spinal cord. This mass extends from the level of the obex inferiorly to the T4 vertebral body. The maximum bulk of the mass is present from C3 to T3 levels. This mass produces remodeling of the posterior vertebral bodies most notably at C4 to C7. (C) T2 weighted sagittal MRI showing an expansile intramedullary mass lesion present within the cervical spinal cord. (D) Post-contrast T1 weighted axial MRI showing an enhancing expansile intramedullary mass lesion present within the central portion of the spinal cord. (E) Post-contrast T1 weighted axial MRI showing a ring-enhancing expansile intramedullary mass lesion present within the central portion of the spinal cord. (F) Moderate to focal densely cellular neoplasm with moderately hyperchromatic and pleomorphic loosely arranged astrocytic cells, with focal marked microvascular proliferation (H&E stain; 200X). (G) Areas of necrosis within the astrocytic neoplasm. No pseudopalisading is appreciated (H&E stain; 100X). (H) Moderate to focal densely cellular neoplasm with moderately hyperchromatic and pleomorphic astrocytic cells, with more than one mitosis in one high-power field, and with focal moderate microvascular proliferation (H&E stain; 400X). (I) Moderately hyperchromatic and pleomorphic astrocytic cells, with more than one mitosis in one high-power field (H&E stain; 400X). (J) Irregular infiltration of diffusely immunopositive neoplastic astrocytic cells, with negative images of hyperplastic vessels (GFAP stain; 100X). (K) The tumor shows a high Ki67 (MIB1) immunohistochemical nuclear labeling index of up to about 20% (Ki67 stain; 200X). (L) The tumor shows a negligible p53 immunohistochemical nuclear labeling index of less than 5% (p53 stain; 200X).
expansive ISC mass, with signal intensity compatible with either low-grade astrocytoma or ependymoma on T1 weighted images. Others were exophytic with features suggesting meningioma. Both current cases showed enhancing ISC masses on MRI that were worrisome for high-grade glioma.

Surgical resection

In low-grade non-infiltrative tumors such as ependymomas or pilocytic astrocytomas, radical excision using recent microsurgical advances before the onset of significant disability is the standard of care and often results in improved risk-benefit ratio, and a good long-term prognosis. However, in high-grade tumors, the value of surgery is less clear. In pediatric intracranial malignant astrocytomas, significant improvement in progression-free survival (PFS) has been reported following radical tumor resection. The data in pediatric ISC tumors are debatable. In some studies, gross total or subtotal resection could be achieved in a majority of patients with minimal short-term morbidity, and cordotomy was also associated with improved survival. However, radical tumor resection of high-grade spinal cord gliomas has not been shown to alter the relentless clinical deterioration and short overall survival of this devastating tumor, and instead carries the risk of permanent neurological sequelae and impairment of the quality of the patients' brief remaining lives. The current recommendation in high-grade ISC tumors is diagnostic biopsy followed by postoperative radiation therapy, and to reserve extensive surgery for anaplastic astrocytomas and palliation in patients in whom RT is not well-tolerated or contraindicated. The rationale behind radical surgery in select cases of high-grade spinal cord gliomas includes obtaining adequate tissue for diagnosis, cyrotective tumor debulking, and helping relieve pain. In our study, although both patients had a similar poor outcome, the histological diversity, with a small cell component resembling PNET in case #1, lack of overt high-grade cytology on frozen sections in case #2, and the resulting need to establish correct diagnosis along with debulking justify maximal safe resection.

Pathological features

Histological type and grade are the most important prognostic factors in ISC glioma. The histopathological features of ISC-GBM are identical to intracranial tumors in adults, except for possibly increased leptomeningeal involvement owing to proximity to the subarachnoid space. The current cases showed a wide histological spectrum ranging from PNET-like areas in case #1 to relatively bland areas in case #2. The predictive value of MIB-1 labeling index is unclear, with no statistical-ly significant difference in outcome between cases with MIB-1 labeling index above and below 5%. In our report, both cases were associated with high Ki67 labeling indices. Pediatric high-grade gliomas in children over three years of age have been found to have a higher frequency of TP53 mutations and overexpression (40%), indicating potential existence of two different molecular pathways of tumorigenesis. The relationship of p53 overexpression to progression to GBM, worse progression-free survival, and brain metastases in spinal GBM found in some studies, were not reproduced in other studies. In our two cases, p53 immunohistochemical labeling indices were different (70% in case #1 vs. 5% in case #2), yet they had similar overall survival of 14 months.

Adult GBM shows a characteristic range of cytogenetic abnormalities that occur at high frequency in subsets of tumors. Loss of chromosome 10, deletion of the p16 gene in 9p21 (often homozygous) amplification of the EGFR locus, and gain of chromosome 7 are among the most common events seen in these tumors. None of these cytogenetic abnormalities, or any others less frequent but typical of adult GBM, were seen in case #1 described in this report. Our findings correlate with pediatric glioblastomas in general and are similar to other recent reports on pediatric GBM. Although losses involving 8p, 16p, and 16q are reported occasionally in adult GBM, they are not frequent in pediatric GBM. Losses involving the long arm of chromosome 19 are also infrequent and more typically found in anaplastic oligodendroglioma. In fact, losses involving 8p and 16q are far more typical of medulloblastomas. From a genetic standpoint, therefore, the pediatric GBM described here is more typical of pediatric brain tumors than adult GBM.

Radiation therapy

Radiation therapy (RT) provides temporary clinical and radiographic improvement, and prolongs survival in high-grade gliomas for some pediatric patients, yet it is rarely curative. An exception is infants and children under three years of age in whom adjuvant treatments are reserved for tumor recurrence. The risk of post-radiation growth suppression or second malignancy following treatment of non-infiltrative spinal cord tumors such as ependymomas or pilocytic astrocytomas is not an issue in high-grade gliomas owing to their short life span. In current treatment protocols, adult patients with high-grade gliomas receive 5,400-6,000 cGy local radiation to the brain tumor bed, with a peri-tumoral margin to account for tumor infiltration, in daily fractions of 180-200 cGy. The spinal cord is less tolerant of radiation, so the radiation dose was restricted to 5040 cGy in both our patients, to avoid the risk of transverse myelitis. As RT is now considered to be the standard management in infiltrative high-grade ISC astrocytomas, and many such patients present with near paraplegia, higher doses up to 5840 cGy have been reported in the literature. However, when used in conjunction with chemotherapy or potential radiosensitizer (TMZ), a lower dose of radiotherapy is reasonable. In a recent study, patients with infiltrative spinal cord astrocytomas who received postoperative RT to a dose of >3500 cGy had a significantly better survival than those with a lesser dose or no RT. Considering the wide range of radiation dose reported (Table 1), the dose is best individualized.
(39%) compared to cerebral GBM (27%) indicates CSF spread as a more important cause of death than direct brainstem involvement, thereby necessitating regular MRI and CSF cytology. In our cases, preoperative CSF cytology did not show neoplastic cells. The patients died from complications of respiratory failure, likely a result of MRI-detected local tumor recurrence and brainstem involvement.

**Conclusions**

The spinal cord is a rare site of pediatric GBM, which has a poor overall survival despite multimodality therapy. The novel aspects of the study include diverse histological spectrum, treatment with Children’s Oncology Group protocol ACGS0126, and relatively unique CGH findings, which correlate with pediatric GBM in general. Diagnostic biopsy followed by radiation without chemotherapy is the standard of care with the option of radical surgery considered based on judicious assessment of risk-benefit ratio. The finding of relatively unique genotypic abnormalities resembling pediatric embryonal tumors in one of the cases presented here highlights the potential value of genome-wide profiling in the development of effective treatment strategies.

**References**