Spinal Cord Diffuse Midline Glioma in a 4-Year-Old Boy

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Abstract
Objective: We report a child presenting with spinal myelopathy secondary to H3K27M mutant diffuse midline glioma.
Case Report: A 4-year-old boy presented with a 3-week history of progressive gait difficulty. Examination revealed bilateral hand and lower extremity weakness, left leg hypertonia with ankle clonus, and a right hemisensory deficit. Magnetic resonance imaging of neuroaxis showed cervical and thoracic spinal cord with expansion and irregular areas of enhancement. Serum and cerebrospinal fluid studies were unremarkable for infectious, autoimmune, inflammatory, and neoplastic causes but showed mild cerebrospinal fluid pleocytosis, hypoglycorrhachia, and high protein level. A thoracic cord biopsy revealed a diffuse midline glioma (World Health Organization grade IV). Consequently, the tumor involved intracranial structures and patient died within 4 months after diagnosis. Conclusion: High-grade spinal cord gliomas are very rare but should be considered in the differential diagnosis of pediatric myelopathy. Tissue biopsy is recommended in indeterminate cases to facilitate diagnosis and to guide management.

Keywords
diffuse midline glioma, glioblastoma, H3K27M mutation, spinal cord disorders, pediatrics

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Background
Primary spinal cord neoplasms account for approximately 1% of all pediatric central nervous system tumors, with astrocytoma being the most common pathological subtype.1,2 Extramedullary spinal tumors are more common in adult populations (80% of cases); however, in the pediatric population, intramedullary tumors are encountered more often.3 Low-grade astrocytomas are the most commonly reported histological type of intramedullary tumors in children (50%-80% of cases). High-grade gliomas are only reported in 1% to 3% of cases, with the remainder being nonglial tumors.4 A spinal glioblastoma is a very rare entity in the pediatric population, and literature describing spinal glioblastomas in children is quite limited. Nevertheless, it should be considered in the differential diagnosis of indeterminate cases of pediatric myelopathy. In this article, we describe a unique case of spinal myelopathy secondary to diffuse midline glioma, K27M mutant with histologic features of glioblastoma in a 4-year-old boy.

Case Report
A 4-year-old previously healthy boy presented with a 3-week history of progressive gait difficulties. He was observed to have gait incoordination for a few days before he started complaining of neck and lower extremity pain. On the day of presentation, he was unable to move his legs upon awakening. There was no history of bladder or bowel dysfunction. Family

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members confirmed that he had not been recently ill or received any recent vaccinations. On examination, he was alert and oriented. He did not have any cranial nerve deficits. He had full upper extremity strength with the exception of mild bilateral grip weakness. He did not have any antigravity movements in the lower extremities. His sensory examination was remarkable for minimal withdrawal to pain bilaterally, increased tone in the left lower extremity, a right hemisensory deficit (to light touch) up to second thoracic dermatomes, and diminished pain sensation in both lower extremities. Deep tendon reflexes were 3+ at quadriceps, and sustained clonus was noted at the left ankle along with bilaterally positive Babinski reflex. Magnetic resonance imaging (MRI) of the neuroaxis showed an abnormal appearance of the cervical and thoracic spinal cord with expansion and irregular areas of enhancement (Figure 1). Initial MRI brain was unremarkable (Figure 2A and B). Routine serum and cerebrospinal fluid studies were performed to look for infectious, autoimmune, inflammatory, and neoplastic etiologies. Routine cerebrospinal fluid studies showed a WBC count of 20/μL (66% lymphocyte), 1 RBC, glucose of 30 mg/dL, and protein of 5875 mg/dL. Infectious workup (including HSV, HHV6, enterovirus, EBV, mycoplasma, Bartonella polymerase chain reactions, and screening tests for tuberculosis) was unremarkable. Autoimmune (ANA, anticardiolipin,
antiphospholipids) and central nervous system inflammatory workup (MS profile, AQ4 Ab, ACE level) were also unrevealing. Cerebrospinal fluid flow cytometry did not show abnormal cells. Given the difficulty in determining an exact onset of symptoms and that apparent abruptness of loss of function, a biopsy was deferred, and on hospital day 2, the patient was started on high-dose intravenous methylprednisolone (30 mg/kg/d) which was continued for a total of 7 days. On the third day of admission, the patient developed respiratory failure requiring intubation and mechanical ventilation along with further progression of muscle weakness in upper extremities. Given the lack of response to treatment, a thoracic cord biopsy was performed (hospital day 4). Preliminary pathological examination was indeterminate, requiring consultation with outside pathologists and taking several weeks for a definitive diagnosis. Therefore, the patient was started on a steroid taper, received intravenous immunoglobulin, and underwent plasma exchange without significant improvement, due to a remote possibility of the lesion being autoimmune. After several weeks, the pathology specimen examination revealed the diagnosis of diffuse midline glioma (World Health Organization [WHO] grade IV; Figure 3). Radiation and chemotherapy with temozolomide and bevacizumab (Avastin) were initiated. Subsequently, the child regained some upper extremity muscle power (coinciding with some improvement in spinal imaging showed in Figure 4), but still remained profoundly weak in his

**Figure 3.** Microscopic examination demonstrates a moderately cellular glial neoplasm with a nodular growth pattern (A, ×10); the tumor cells have irregular, hyperchromatic nuclei, and scant cytoplasm (B, ×40); occasional mitotic figures are identified (C, ×40); the Ki-67 proliferation index is estimated at up to 12% (D, ×10); glial fibrillary acidic protein (GFAP) immunoreactive is shown in tumor cells (E, ×40); an immunostain for H3K27M mutant protein shows strong nuclear positivity.
lower extremities. The patient also required a tracheostomy to maintain the airway but died within 4 months after diagnosis as a result of intracranial spread of this metastatic disease (Figure 2C and D).

Discussion

Pediatric spinal cord glioblastoma is a very rare entity with few cases reported in the literature. The cervical region is the most commonly affected area of the spinal cord. Clinical presentation is variable based on the region of the spinal cord involvement and tumor growth rate (which is irrespective of the histopathological subtype of tumor). The most commonly documented presenting symptom of a primary spinal canal tumor is pain, which may be present long before the manifestation of any neurological deficits. The other common symptoms in the pediatric population include motor weakness, gait abnormalities, and bowel and bladder issues. Our patient presented following a subacute course of gait abnormalities before the presentation of pain, although determining the true onset of symptoms was difficult to elicit upon presentation. Neuroimaging and laboratory workup including serum and cerebrospinal fluid studies are imperative in the evaluation of these symptoms to rule out various other more common etiologies of myelopathy including infection, autoimmune processes, and inflammation. Typical MRI finding of a spinal high-grade neoplasm includes hemorrhage involving the lower pole, so-called “cap sign,” the presence of multiple cysts, and leptomeningeal involvement. Our patient did not fit the typical imaging feature of high-grade neoplasm, and while portions of the workup were pending, high-dose methylprednisolone therapy was initiated due to concern for inflammatory etiology. Given worsening of clinical condition, biopsy was deemed necessary. Preliminary pathological examination was inconclusive, and patient was empirically treated with intravenous immunoglobulin and plasmapheresis due to clinical suspicion for an autoimmune etiology, while awaiting more detailed pathology workup. After consultation with colleagues in neuropathology department at the University of California San Francisco, the ultimate diagnosis of diffuse midline glioma (WHO grade IV) was made based on morphology and immunoprofile, especially positive nuclear stain for H3K27M. Diffuse midline gliomas, H3K27M mutant, are genetically characterized by mutations in the histone H3-encoding genes. The vast majority of diffuse midline glioma demonstrates astrocytic differentiation with classic morphologic features of glioblastoma as seen in the current case. Patient was started on combination of radiotherapy and chemotherapy.

We propose that if the etiology of a myelopathy in a pediatric patient is unclear, with radiographic findings indicative of a space occupying lesion, a tissue biopsy should be sought to facilitate diagnosis and guide management. Although seemingly obvious in retrospect, it may be difficult to prioritize a biopsy, particularly if the onset of symptoms is not clear. Moreover, pathologic confirmation of a neoplasm may be quite difficult, requiring multiple consultations. Overall, pediatric glioblastoma has a very dismal prognosis with patient survival ranging from 4 to 16 months (median survival of 12 months). Rarely, patients may live longer (as an exceptionally long survival of 144 months was reported for a single patient with spinal glioblastoma). In the pediatric population, the extent and location of the lesion as well as the feasibility of a gross
total resection are the most important factors affecting the prognosis. In the end, survival remains poor. Finally, intensive rehabilitation may help empower these patients to achieve an improved quality of life.

**Author Contributions**

AK, SR and LSD contributed to conception and design. All authors contributed to acquisition, analysis, or interpretation of data. AK, SR and LSD drafted the manuscript. All authors critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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**Ethical Approval**

Not applicable.

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