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Case Report

Primary spinal intramedullary anaplastic ganglioglioma in a pediatric patient

Huy Dang[1], Abdul Basit Khan[1], Nisha Gadgil[2], Marc Prablek[1], Frank Y. Lin[3], Melissa M. Blessing[4], Guillermo Aldave[2], David Bauer[2]

[1]Department of Neurosurgery, Baylor College of Medicine, [2]Department of Neurosurgery, Baylor College of Medicine/Texas Children's Hospital, [3]Department of Pediatric Hematology-Oncology, Baylor College of Medicine, Texas Children's Cancer Center, Dan L Duncan Cancer Center, [4]Department of Pathology, Baylor College of Medicine/Texas Children's Hospital, Houston, United States.

E-mail: Huy Dang - huyqdang1997@gmail.com; Abdul Basit Khan - basit.khan@bcm.edu; Nisha Gadgil - nisha.gadgil@bcm.edu; Marc Prablek - marc.prablek@bcm.edu; Frank Y. Lin - fylin@texaschildrens.org; Melissa M. Blessing - mmblessi@texaschildrens.org; Guillermo Aldave - gxaldave@texaschildrens.org; *David Bauer - dfbauer@texaschildrens.org

***Corresponding author:**
David Bauer,
Department of Neurosurgery,
Baylor College of
Medicine/Texas Children's
Hospital, Houston,
United States.

dfbauer@texaschildrens.org

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ABSTRACT

Background: Gangliogliomas (GGs) are rare tumors of the central nervous system composed of neoplastic neural and glial cells and are typically low-grade. Intramedullary spinal anaplastic GGs (AGG) are rare, poorly understood, and often aggressive tumors that can result in widespread progression along the craniospinal axis. Due to the rarity of these tumors, data are lacking to guide clinical and pathologic diagnosis and standard of care treatment. Here, we present a case of pediatric spinal AGG to provide information on our institutional approach to work-up and to highlight unique molecular pathology.

Case Description: A 13-year-old female presented with signs of spinal cord compression including right sided hyperreflexia, weakness, and enuresis. Magnetic resonance imaging (MRI) revealed a C3-C5 cystic and solid mass which was treated surgically with osteoplastic laminoplasty and tumor resection. Histopathologic diagnosis was consistent with AGG, and molecular testing identified mutations in *H3F3A* (K27M), *TP53*, and *NF1*. She received adjuvant radiation therapy and her neurological symptoms improved. However, at 6-month follow-up, she developed new symptoms. MRI revealed metastatic recurrence of tumor with leptomeningeal and intracranial spread.

Conclusion: Primary spinal AGGs are rare tumors, but a growing body of literature shows some trends that may improve diagnosis and management. These tumors generally present in adolescence and early adulthood with motor/sensory impairment and other spinal cord symptoms. They are most commonly treated by surgical resection but frequently recur due to their aggressive nature. Further reports of these primary spinal AGGs along with characterization of their molecular profile will be important in developing more effective treatments.

Keywords: Anaplastic, Case report, Ganglioglioma, Spinal

INTRODUCTION

Gangliogliomas (GGs) are tumors of the central nervous system (CNS) that arise from glioneuronal precursors. Histologically, they are composed of both neoplastic glial and neural components, with the glial component proliferating and most often driving the tumor pathophysiology.[13] The World Health Organization (WHO) tumor classification is based on the degree of malignancy of the glial component. The majority of these tumors are benign and classified as the WHO Grade 1 tumors. Anaplastic GGs (AGGs) are also reported and, while less

well defined, are regarded as the WHO Grade 3 malignant tumors.[11] Anaplastic transformation occurs in 4–5% of all GGs with a median survival of approximately 29 months. This happens most commonly in the glial component and leads to cellular and vascular proliferation alongside focal necrosis.[16,19]

Intramedullary/spinal GGs are most often found in the cervical and thoracic spine with symptoms associated with neuroaxis dysfunction in sensation, motor control, and pain.[5] Spinal GGs are rare, only making up 1% of all adult spinal tumors but comprising nearly 30% of tumors in patients under 3 years.[5,16] Intramedullary AGGs are rarer still with a scoping review conducted by Vlachos *et al*. finding only 22 reported cases in the literature.[26] They mostly affect children and young adults (median age of 14 years) but otherwise have no predilection for race or sex.[17] Due to the rarity of intramedullary AGGs, little is known about demographics, diagnostic workup, treatment, or long-term survival for these patients. We present a case of intramedullary AGG in a pediatric patient here to add to the limited existing literature.

CASE DESCRIPTION

History and presentation

A developmentally normal 13-year-old African American female with a history of attention deficit hyperactivity disorder and mild scoliosis presented for evaluation of new onset right elbow contracture. Three years prior, she experienced a sudden inability to straighten her right elbow and simultaneously developed stiffness and pain in the right shoulder. Acutely, she reported recurring episodes of enuresis, concerning for spinal cord pathology. She has no significant family history pertaining to presentation. Physical examination revealed hyperreflexia of her right upper (3 +) and lower extremity (4 + with clonus and positive Babinski reflex). She had right upper and lower extremity weakness (4/5 strength), decreased bulk, and increased tone. No evidence of dysmetria, ataxia, or changes in gait. Magnetic resonance imaging (MRI) of the cervical spine revealed a 4.1 × 1.2 × 1.5 cm mixed cystic and solid intramedullary mass spanning C3-C6 with cord edema extending superiorly and inferiorly to these levels [Figure 1a]. An osteoplastic laminoplasty with tumor resection was performed.

Surgical procedure

Cervical C3-6 laminectomy was performed followed by semi-laminectomy of inferior C2 and superior C7. A key technical nuance is to perform adequate bony exposure to afford a generous operative window for the tumor. Next, epidural ultrasound was used to identify the tumor, which appeared mixed density but generally hyperechoic. The dura

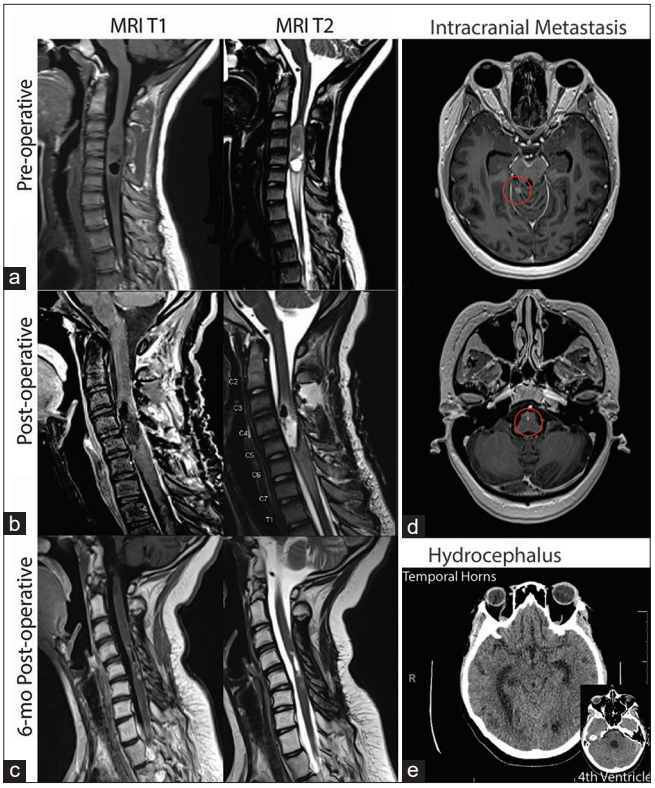

Figure 1: Magnetic resonance imaging T1 and T2 sequences at (a) preoperative, demonstrating cord expansion suspicious for the presence of a tumor; (b) postoperative, demonstrating gross total resection and subtle enhancement along the posterior aspect of the cord, and (c) 6-month post-operative, demonstrating new leptomeningeal enhancement concerning for metastatic spread of disease. (d) 8-month postoperative (T1 with contrast) demonstrating intracranial metastasis (circled in red) in the cerebellum and brainstem. (e) 8-month postoperative (T1) demonstrating hydrocephalus in the temporal horns of the lateral ventricles and the fourth ventricle.

was opened and then direct stimulation was used for dorsal column mapping. Physiologic midline was identified with stimulation, which corresponded to an anatomic midline. After midline myelotomy, we exposed tumor which appeared gray and firm. We exposed the rostral and caudal extent of the tumor. The tumor was biopsied, and then microsurgical technique with an ultrasonic aspirator was used to debulk and resect the tumor. Gross total resection (GTR) of the tumor was achieved without any residual tumor as confirmed by intraoperative ultrasound and visual inspection. Laminoplasty was then performed and previously removed laminae reapproximated. Intraoperative neuromonitoring was used to maximize tumor resection and minimize neurological morbidity.[25] No complications arose during surgery.

Postoperative care and follow-up

Immediate postoperative MRI showed GTR of tumor. The patient did have new temporary worsening deficits in

strength, endurance, balance, and mobility after surgery. She remained inpatient for approximately 2 months for rehabilitation, making good recovery. She then received adjuvant proton beam radiation therapy to the C2-7 tumor bed at a dose of 50.4 Gy (relative biological effectiveness). The family declined chemotherapy, including a trial of temozolomide or other early phase therapeutic studies, after careful consideration with the clinical team. At 3-month follow-up, she reported that her weakness and muscle deficits were improved with physical therapy, but she had developed new onset of upper back pain that began around the time she started radiotherapy. MRI at 1 month revealed subtle enhancement around the surgical resection site that may indicate postsurgical scar tissue [Figure 1b]. Approximately 6 months after surgery, she presented with headaches, vomiting, behavioral changes, and new seizure activity. New MRI demonstrated disease progression with leptomeningeal enhancement in the thoracic and lumbar spine [Figure 1c], intracranial metastasis [Figure 1d], and hydrocephalus [Figure 1e]. She received medication to control her headaches and seizures, a ventriculoperitoneal shunt for the hydrocephalus, and additional radiation therapy to the untreated locations of disease. She enrolled in hospice care and died of disease 11 months after the date of GTR.

Pathologic diagnosis

Histologic analysis showed a pleomorphic neoplasm with atypical glial and dysmorphic neuronal cells, some of which displayed binucleation [Figure 2a]. In addition, there was an area of hypercellularity with increased atypia [Figure 2b], consistent with anaplastic transformation, and presence of mitoses (focally up to 8 mitotic figures per ten high-power fields). Glial fibrillary acidic protein (GFAP) highlighted neoplastic glial cells [Figure 2c] and synaptophysin highlighted neoplastic neurons [Figure 2d]. Immunohistochemistry additionally showed strong and diffuse nuclear staining for p53 in 90–100% of cells consistent with a mutational profile, and increased Ki-67 proliferation rate in 70–80% cells in the anaplastic region. While the most recent edition of the WHO classification of tumors of the CNS does not establish definitive histologic or molecular diagnostic criteria for AGG,[29] the presence of markedly increased mitotic activity and accompanying proliferative index warranted that diagnosis. Tumor molecular profiling with the Texas Children's Hospital Solid Tumor Comprehensive deoxyribonucleic acid/ribonucleic acid panel revealed mutations in: *H3F3A* K27M (c.83A>T, p.Lys28Met, allele fraction 31%), *TP53* (c.731_748del, p.Gly244_Pro250delinsAla, allele fraction 41%), and *NF1* (c.3058delG, p.Glu1020LysfsTER2, allele fraction 59%, and c.4245T>A, p.Asn1415Lys, allele fraction 31%). While uncommon and midline tumors with GG morphology and cooccurring *H3F3A* K27M and RAS/mitogen-activated protein kinase (MAPK) pathway mutations have been previously reported;[18] this was felt to be concordant with the histologic diagnosis. Tumor DNA methylation profiling is an emerging molecular technique with promising diagnostic utility for CNS tumors, however, is not yet widely available for clinical use.

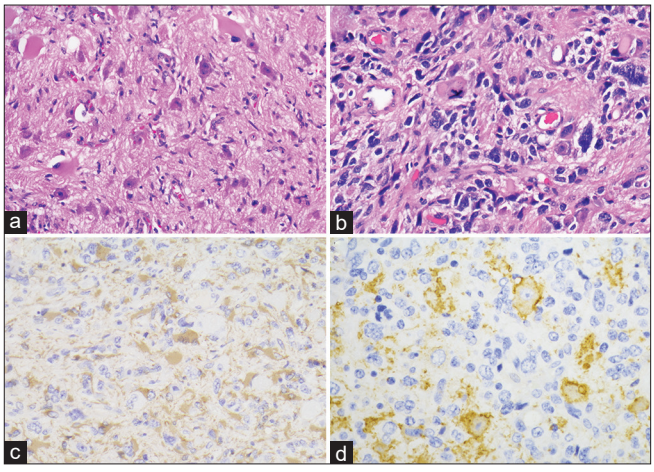

Figure 2: Histologic sections show a fibrillary background with atypical mature appearing neurons, including binucleate forms (a). Other sections have a higher grade component with marked atypia and atypical mitoses (b). Glial fibrillary acidic protein is positive in the majority of neoplastic cells (c), and Synaptophysin highlights an atypical neuronal component (d).

DISCUSSION

Diagnostic strategies

Intramedullary spinal cord tumors can be difficult to localize and require imaging.[26] MRI is the most reliable technique to define the size and extent of AGGs/GGs.[6,26] Some characteristics of AGGs/GGs on MRI include prominent cysts, scoliosis or bone erosion/scalloping, mixed hyper/hypointense signal on T1-weighted images, absence of edema, and patchy enhancement.[19,26] These features are not exclusive to AGGs/GGs and can be observed in astrocytomas and ependymomas, thus imaging alone is insufficient for AGG diagnosis. Due to its nonspecific presentation, intramedullary AGGs should be considered in the differential diagnosis for patients presenting with cord compression symptoms, especially if persistent.

Histopathologically, GGs are diagnosed by the presence of both glial and neuronal neoplastic cells. Immunohistochemistry including GFAP and synaptophysin, respectively, seem to be the most reliable markers to identify the dual population of neoplastic cells.[24] In the spinal cord, distinction between normal neurons entrapped within an infiltrating glioma from neoplastic ganglion cells can be particularly challenging. The presence of binucleated ganglionic cells is rare among normal

neurons and is thus a helpful indicator of a neoplastic neuronal component.[2] This binucleation along with prominent nucleoli is among the most common characteristics of dysplastic ganglionic cells across cases analyzed by Vlachos *et al*.[26] Ganglionic/neuronal cell density within the tumors is highly variable and typically has low mitotic activity. In contrast, the glial portion of the tumor is marked by hypercellularity and high mitotic activity.[30] Ki-67 is a useful proliferative marker for visualizing the degree of mitoses. Together with the clinical symptoms and imaging, these features – a GFAP-positive glial portion with signs of anaplasia and hypercellularity with Ki-67 co-stain and immunohistochemical-proven atypical neuronal component – provide strong evidence for AGG.

AGGs have been historically diagnosed based on histological criteria. However, diagnostic criteria for AGG continues to be challenging, with attempts to categorize tumors by their molecular profiles.[12] A recent study by Reinhardt *et al*., 2022, showed that this diagnosis may be resolved into several distinct tumor types based on molecular characteristics which may carry different prognostic and therapeutic implications.[22] For example, the authors suggest AGGs with H3 mutations could be classified as diffuse midline gliomas (DMGs). However, AGGs do not have a separate methylation class, suggesting that the histological criteria used for diagnosis may represent a heterogeneous group of tumor entities. An "integrated diagnosis" approach, which synthesizes histologic and molecular tumor features is increasingly utilized to create comprehensive, clinically useful, and precise diagnoses. While the most accepted convention for AGGs remains a subject of debate,[10] advances in molecular profiling, and more complex bioinformatic approaches will refine the definition of "AGG" to better account for the current heterogeneity of this histological entity.

Tumor molecular profile

The biologic understanding of pediatric spinal AGGs has been limited by its rare incidence. Alterations involving the MAPK signaling pathway, most frequently *BRAF* p.V600E mutations, have been reported in a majority of GGs.[20] Mutations affecting the histone H3 complex, most frequently the *H3F3A* K27M mutation, have primarily been known as a hallmark of DMGs,[18] but are increasingly being recognized in other low-grade CNS tumor entities. A few reports have noted presence of cooccuring *H3F3A* K27M and *BRAF* p.V600E mutations in midline low-grade GGs;[18] however, our case demonstrates *H3F3A* K27M without *BRAF* p.V600E, with mutations instead involving *NF1*. There is speculation that the BRAF mutation may be lost with anaplastic transformation and may furthermore influence long-term survival if associated with H3F3A K27M.[18] In our case, the MAP-Kinase pathway mutation remained. Based on the present literature, no definitive conclusion can be made about the roles these mutations play in AGG tumorigenesis. The limited available data suggest that *H3F3A* K27M mutation should be assessed in all GGs as it may be associated with clinical progression, anaplastic transformation, metastasis, and poor prognosis.[7,9] On the other hand, circumscribed AGG with *H3F3A* K27M mutation may have superior prognosis to their infiltrative counterparts,[21] and further study is necessary.

TP53 is commonly mutated in many tumors due to its critical role as a cell cycle checkpoint inhibitor. Cancer cells temper this regulation which allows them to over-proliferate and accumulate more mutations.[15] Rare cases of *TP53* mutations have been documented in GGs that underwent malignant progression to glioblastomas.[4,8] However, one case of low-grade GG has been reported to harbor *TP53* mutation.[27]

The *NF1* mutations found in this tumor were believed to cause premature truncation and loss of function of the NF1 protein based on their location. *NF1* loss of function has been observed in many tumor types and results in elevated levels of active GTP-bound RAS and activation of MAP-Kinase and PI3K pathways.[1] These pathways are canonically implicated in tumorigenesis due to their role in cell growth and proliferation. While *NF1* alterations are infrequently reported in GG, this remains concordant with MAPK pathway GG pathogenesis (WHO CNS 2021).[26]

Treatments and outcomes

Surgical excision is the standard of care for AGGs with the goal of GTR, but rate of recurrence is high even after complete removal. Adjuvant radiation or chemotherapy is often recommended, though this is controversial because of the scant evidence for its efficacy.[14,23] Due to the rarity of spinal AGGs in particular, there are no specific guidelines for their treatment. Use of surgery and adjuvant therapy was advocated by Vlachos *et al*. (2/22 achieved progression-free survival; both received combination surgery and adjuvant therapy), although they noted that this should be taken anecdotally.[26] The survival benefit of GTR compared with subtotal resection in treating AGGs has been reported by Mallick *et al*. and Selvanathan *et al*.[14,23] Both studies, however, failed to conclude whether adjuvant therapy improved outcome, most likely due to small sample size. As molecular characteristics of AGGs become further delineated, they may help guide therapy based on the underlying molecular profiles. In our patient's case, the *H3F3A* mutation likely conferred poor prognosis. The therapeutic value of this mutation is limited, though, as it has been uniformly fatal across different treatments.[3] The *NF1* mutation may help predict therapeutic response to targeting the MAPK-pathway;[28] however, targeting cooccuring mutations in tumors driven by H3K27 alterations has not

been successful in limited experience.[26] Chemotherapy was offered to our patient but ultimately declined due to the lack of evidence supporting efficacy.

CONCLUSION

AGGs located in the spinal cord are rare and not well studied. There are currently only 22 cases reported and minimal information available about the genetic profile of AGGs. Our case documents an aggressive spinal AGG that progressed despite surgical resection and adjuvant radiation therapy. Molecular profiling of this tumor revealed genomic mutations including *H3F3A*, *TP53*, and *NF1*. These mutations represent possible prognostic markers, classifiers, and therapeutic targets for the future investigation. As more cases are added to the literature, we look forward to a more well-informed, data-driven approach to recognizing, diagnosing, classifying, and treating this tumor type.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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