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Genetic Characterization of a Multifocal Ganglioglioma Originating Within the Spinal Cord

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Abstract

BACKGROUND—Gangliogliomas are rare, low-grade intra-axial tumors that exhibit both neuronal and glial components. Although the vast majority present as an intracranial lesion, a rare subset exist as isolated lesions of the spinal cord. Gangliogliomas have also been shown to harbor mutations in the p53 tumor suppressor gene and *BRAF* oncogene. Previous studies in ganglioglioma have correlated p53 mutations with histologic transformation and *BRAF* mutations with worse prognosis.

CASE DESCRIPTION—In this report, we describe a 35-year-old female who presented with multifocal ganglioglioma, involving both the conus medullaris and filum terminale. The dominant lesion in the filum terminale was resected, which revealed World Health Organization I grade, p53 mutant, and *BRAF* wildtype status. Our study documents the first report of a multifocal ganglioglioma, originating within the spinal cord.

CONCLUSIONS—Importantly, this case contradicts previous reports of p53 and *BRAF* mutations portending worsened tumor behavior and prognosis and demonstrates that further studies are needed to delineate the role of genetic characterization in the biologic understanding and management of gangliogliomas.

Keywords

BRAF; Ganglioglioma; Multifocal ganglioglioma; p53

INTRODUCTION

Gangliogliomas are rare tumors composed of both neuronal and glial components. They are predominantly low-grade tumors (World Health Organization [WHO] grade I and II), though

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there are anaplastic variants (WHO grade III) that display more aggressive behaviors. The neuronal component is characterized by large, mature neoplastic neurons, and the glial component consists of astrocytic or oligodendroglial cells.¹ The majority of cases present as intra-axial lesions, but in rare instances, gangliogliomas may occur as a primary mass in the spinal cord.

Given their rarity, little is known about the molecular genetics underlying the oncogenesis and progression of gangliogliomas. Recent reports have attempted to clarify the roles of p53 and *BRAF* mutations in ganglioglioma formation and prognosis, but a paucity of data limits the ability to make definitive conclusions. In this report, we describe the first case of a multifocal ganglioglioma of the spinal cord, affecting both the conus medullaris and filum terminale. We discuss the histologic and genetic characteristics of our patient's tumor, as they relate to the current literature surrounding the roles of p53 and *BRAF* mutations in ganglioglioma biology and prognosis.

CASE REPORT

A 35-year-old female presented with a 3-year history of lower back pain, hip discomfort, and numbness and tingling in the legs with intermittent falls. Neurologic examination revealed weakness and impaired vibratory sensation in both lower extremities. Patellar reflexes were decreased on both sides, and Achilles reflexes were decreased on the right side. She had no previous history of malignancy, and her family history was noncontributory.

Magnetic resonance imaging (MRI) of the spine with and without intravenous gadolinium demonstrated at least three foci of homogeneous enhancement, including nodules within the left spinal cord at the level of L1, within the conus medullaris, and just below the tip of the conus medullaris along the expected course of the filum terminale (Figure 1). MRIs of the rest of the entire neuro-axis, including brain, were normal. The patient underwent a lumbar puncture, but this was nondiagnostic based on cytology. As such, the patient was referred for open biopsy with possible resection. In the operating room, an L1–2 laminectomy revealed 2 of the lesions visible on MRI, 1 along the conus and the other within the filum terminale. Intraoperatively, because a safe plane could not be found around the lesion, the mass in the conus was not resected. However, the mass in the filum terminale was removed in total. The patient recovered from surgery uneventfully and was discharged home 2 days later. An MRI of the spine 6 months following surgery demonstrated gross total resection of the mass in the filum terminale and no interval progression of the other nodules (see Figure 1).

Final histopathologic analysis of the excised lesion showed neoplastic tissue with mixed neuronal and glial components. Glial components were appreciated on frozen sections, and hematoxylin-eosin staining revealed several examples of perivascular lymphocyte cuffing, Rosenthal fibers, and cytologically abnormal ganglion cells. Binucleated neurons were visualized using NeuN, neurofilament, and synaptophysin staining. Many of the cells also showed CD34, tau, and ubiquitin immunoreactivity, and some scattered olig2-positive elongated cells were noted, though rare. The Ki-67 labeling index was 1%, and the tissue was diffusely positive for p53 immunohistochemistry. Peri-vascular lymphocyte cuffing and microglial cells were highlighted by CD45 staining. The histologic picture was consistent

with a WHO grade I ganglioglioma (Figure 2). Genomic deoxyribonucleic acid was extracted from tumor tissue for standard direct sequencing of exon 15 of the *BRAF* gene. No mutations were detected in the specimen.

DISCUSSION

Gangliogliomas are rare intra-axial tumors composed of both neoplastic neurons and glial cells. Although intracranial gangliogliomas may disseminate into the spine, only a few cases have been reported as primary ganglioglioma affecting the conus medullaris.² To our knowledge, this is the first report of a primary spinal cord ganglioglioma with multifocal dissemination on initial presentation. In addition to a mass in the conus medullaris, our patient had a separate lesion in the filum terminale. Gross total resection is the treatment of choice for WHO grade I and II gangliogliomas, and prognosis for patients with gross total resection is excellent.^{3–5} To the best of our knowledge, only 5 cases with multifocal benign (WHO grade I or II) ganglioglioma exist in the literature,^{6–10} all of which were located in the brain (one with extracranial in addition to intracranial presentation). Thus no guidelines currently exist regarding treatment of these multifocal lesions. Of the 5 previously reported cases, one received gross total resection of all lesions; 2 received resection of some, but not all, lesions; and 2 cases were stereotactically biopsied. All patients described tolerated their treatment and were alive at the time of publication of the respective reports. In our patient, a safe resection plane around the lesion in the conus could not be found. Furthermore, given that the MRI indicated multifocal disease, resection of the filum tumor to achieve diagnosis while minimizing neurologic risk was felt to be the optimal surgical strategy.

Our patient's presentation is in stark contrast to previous cases of gangliogliomas affecting the conus medullaris, which have all presented as solitary lesions.² Interestingly, despite its locally disseminated presentation, the tumor in our patient was histologically designated as WHO grade I. A single retrospective review suggested that radiation therapy may provide improved local control in subtotally resected low- and high-grade single ganglioglioma, but no overall survival benefit was demonstrated.¹¹ As such, further medical treatment or radiotherapy was deferred in favor of active surveillance. Salvage radiation therapy remains an option for our patient in the case of recurrence of the resected tumor.^{11,12}

Despite its benign histologic grading, our patient's tumor exhibited features characteristic of higher-grade tumors, including multifocal presentation and p53 mutation. p53 mutations in gangliogliomas have been associated with progression toward higher WHO grades and even transformation into glioblastoma.^{13–15} Previous studies have suggested that p53 mutations may be unique to higher-grade (i.e., WHO II–IV) gangliogliomas and contribute to dedifferentiation and tumor progression from WHO grade I.^{13,16} However, the present case demonstrates that p53 mutations may occur in WHO grade I tumors and suggests that this finding is not necessarily associated with increased mitotic activity and malignant transformation.

BRAF is an intracellular serine/threonine kinase component of the mitogen-activated protein kinase (MAPK) pathway.¹⁷ Ras activates *BRAF*, which leads to downstream promotion of cell growth, survival, and differentiation. A common mutation in *BRAF*, c.1799T>A

(p.V600E), causes constitutive activation of *BRAF* and can lead to increased oncogenicity. Approximately 20%–25% of gangliogliomas harbor the *BRAF* mutation, although reports have varied between 18% and 57%.^{17–19} However, the prevalence of *BRAF* mutations in primary spinal cord gangliogliomas is unknown, due to their rarity.^{17–19} It has been suggested that *BRAF* mutations may predict increased tumor aggression and be a negative prognosticator in gangliogliomas.^{20,21} Lummus et al²² reported 2 cases of solitary gangliogliomas that progressed with metastatic spread in the spinal cord and leptomeninges that were *BRAF* wildtype. Our patient's tumor also presented with a similarly aggressive MRI appearance as multifocal lesions, despite being *BRAF* wildtype. As such, further studies are required to delineate the exact role of *BRAF* mutations in the prognostication of spinal cord gangliogliomas.¹⁷

In conclusion, we present a case of a multifocal ganglioglioma originating within the spinal cord that affected both the conus medullaris and filum terminale. Importantly, despite our patient's tumor being p53-mutated and *BRAF*-wildtype, the tumor was graded as WHO grade I, which contradicts previous reports correlating p53 mutations and *BRAF* mutations with increased tumor grade and clinical aggression. In order to appropriately identify patients at higher risk of ganglioglioma transformation and worse prognosis, more data are needed to link genetic markers to anaplastic changes in gangliogliomas.

Abbreviations and Acronyms

<i>BRAF</i>	Serine/threonine-protein kinase B-Raf
MRI	Magnetic resonance imaging
WHO	World Health Organization

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Figure 1.

(A) Sagittal view of T1-weighted lumbar spine magnetic resonance imaging (MRI) after contrast administration demonstrating 2 dominant, homogenously enhancing masses within the spinal canal (*arrows*). Other masses not shown. (B) An axial slice from the same T1-weighted postcontrast MRI redemonstrates the enhancing mass within the filum terminale (*arrow*). (C) Sagittal view of a T1-weighted lumbar spine MRI after contrast administration taken 6 months after surgery demonstrating postoperative changes (*arrow*) and no evident changes in the remaining lesions.

Figure 2. Representative low-power (20× magnification, *top row*) and high-power (40× magnification, *bottom row*) views of the resected tumor showing characteristics of World Health Organization grade I ganglioglioma, stained for (A) hematoxylin-eosin, (B) Ki-67, and (C) p53 immunohistochemistry.