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BRIEF REPORT

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Molecular characterization reveals *NF1* deletions and *FGFR1*-activating mutations in a pediatric spinal oligodendroglioma

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Abstract

Pediatric spinal oligodendrogliomas are rare and aggressive tumors. They do not share the same molecular features of adult oligodendroglioma, and no previous reports have examined the molecular features of pediatric spinal oligodendroglioma. We present the case of a child with a recurrent spinal anaplastic oligodendroglioma. We performed whole exome (paired tumor and germline DNA) and transcriptome (tumor RNA) sequencing, which revealed somatic mutations in *NF1* and *FGFR1*. These data allowed us to explore potential personalized therapies for this patient and expose molecular drivers that may be involved in similar cases.

KEYWORDS

anaplastic oligodendroglioma, fibroblast growth factor receptor type 1, molecular sequence data, *NF1*, precision medicine, spinal cord neoplasms

1 | INTRODUCTION

Spinal cord oligodendrogliomas are very rare tumors, comprising <5% of spinal cord tumors in all ages.[1–5] In children, spinal tumors are even less common, with spinal gliomas accounting for only 1–3.5% of all pediatric central nervous system (CNS) tumors; only a few cases and one case series of two spinal oligodendrogliomas have been reported in the pediatric population.[3,5,6] While standard treatment consists of surgical resection, alkylating chemotherapy, and radiation therapy, there is no consistently followed regimen given the rarity of pediatric high-grade spinal oligodendrogliomas.

The field of neuro-oncology is increasingly moving toward personalized treatment options for patients. The molecular analysis of adult gliomas by numerous investigators has resulted in the identification of several cytogenetic markers that confer varying prognostic benefits and therapeutic responses.[1,7] However, these features (e.g., 1p/19q codeletion) are less informative in the pediatric glioma setting.[8] Furthermore, the molecular features of pediatric spinal oligodendroglioma specifically have not previously been examined. We present a case of a child with a spinal anaplastic oligodendroglioma (AO) and discuss our investigation of potential targeted agents using tumor sequencing data.

Abbreviations: AO, anaplastic oligodendroglioma; ATRX, alpha thalassemia/mental retardation syndrome X-linked; CNS, central nervous system; FGFR, fibroblast growth factor receptor; HGG, high-grade glioma; IDH, isocitrate dehydrogenase; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; MGMT, O-6-methylguanine-DNA methyltransferase; MRI, magnetic resonance imaging; NF1, neurofibromatosis type I

2 | RESULTS

A 3-year-old female child presented with a 2-month history of neck pain, left leg weakness, asymmetric gait, and right head tilt. Spinal magnetic resonance imaging (MRI) revealed a 6 × 1 cm enhancing intramedullary mass extending from C4 to T4. She underwent uncomplicated subtotal resection of the primary tumor (Fig. 1A). Total resection was avoided due to intimate involvement of the tumor with the spinal cord. Her gait had improved by 1 week after surgery. Pathology revealed a grade III AO with a Ki-67 tumor cell proliferative index of 10–25%. FISH was negative for 1p/19q codeletion. She underwent adjuvant chemotherapy with 18 cycles of oral temozolomide, but when a 3-month surveillance MRI suggested tumor progression, temozolomide was reinitiated for nine additional cycles. Surveillance MRIs remained stable for 3 years from discontinuation of chemotherapy, when she developed progressive neck pain and weakness in both legs. Repeat MRI revealed tumor progression as an enhancing lesion spanning C5–T2, with a nodular enhancing focus at C4, progression of edema to C2–C3, and a syrinx from the lower cervical spine to the conus (Fig. 1B).

She underwent subtotal resection of the recurrent tumor and syrinx decompression via syringo-subarachnoid shunt placement. Lower extremity weakness improved postoperatively with no new deficits. Recurrent tumor pathology remained AO, with microvascular proliferation and a Ki-67 of 4%, isocitrate dehydrogenase (IDH) mutation negative, O-6-methylguanine-DNA methyltransferase (MGMT) promoter unmethylated, alpha thalassemia/mental retardation syndrome X-linked (ATRX) preserved, and p53 not overexpressed (Figs. 1C and 1D). Restaging studies with brain MRI and cerebrospinal fluid cytologic analysis were unremarkable. Total spine MRI 2 weeks after surgery showed decreased size of the syrinx and stable residual tumor. She underwent conformal proton radiotherapy with 50.4 GyE to the resection bed and vertebral bodies, but she subsequently developed acute radiation necrosis and back pain, which has responded well to steroids and bevacizumab.

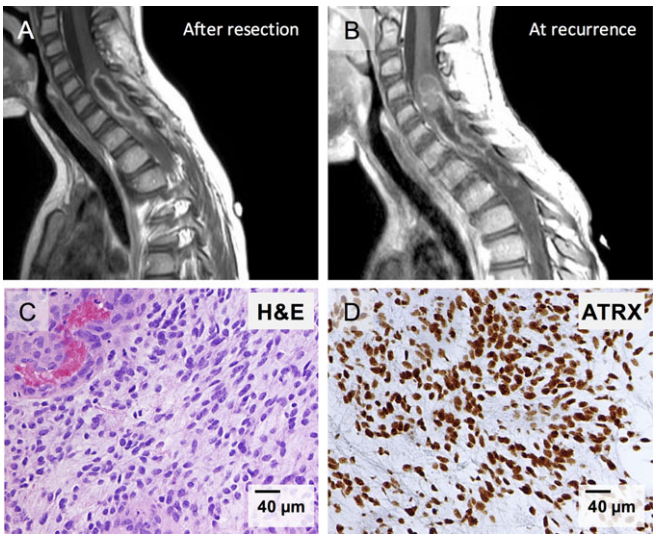

FIGURE 1 Spinal oligodendroglioma imaging and pathology. (**A**) Spinal MRI, sagittal image, T1 series postcontrast, illustrating tumor after initial resection. (**B**) Spinal MRI, sagittal image, T1 series postcontrast, showing recurrent disease in the cervical spine, primarily in the C4-T2 region. (**C**) Tumor parenchyma shows histologic findings on hematoxylin and eosin stain consistent with grade III anaplastic oligodendroglioma: focal high density of round to spindled cells; many cells with perinuclear halos; scattered dark and angulated anaplastic nuclei; two large areas of microvascular proliferation at the left side of the figure; and microcysts filled with mucin are prominent near the lower right corner of the figure. (**D**) Alpha thalassemia/mental retardation syndrome X-linked (ATRX) protein is preserved in nuclei of vascular cells and neoplastic cells (ATRX loss is frequently seen in *ATRX*-mutated astrocytoma).

At the time of recurrence, the patient was enrolled on PEDS-MIONCOSEQ, a precision oncology study involving whole exome (paired tumor and germline DNA) and transcriptome (tumor RNA) sequencing. Clinically integrated sequencing was performed according to previous published methodology.[9] Nucleic acid preparation, high-throughput sequencing, and computational analysis were performed using standard protocols in our sequencing laboratory in the Michigan Center for Translational Pathology, which adheres to the Clinical Laboratory Improvement Amendments.

Sequencing revealed a somatic point mutation and three small deletions in *NF1*, consistent with biallelic inactivation (Supplementary Table S1). There was no evidence of germline *NF1* alterations, skin lesions, or family history suggestive of neurofibromatosis type I (NF1). Sequencing also revealed two somatic activating missense mutations in *FGFR1* (Supplementary Table S2). No mutations in *BRAF* were observed, which are recurrently found in some oligodendrogliomas.[10] Sequencing results were otherwise unremarkable (Supplementary Fig. S1). Results of her tumor sequencing were discussed in our multidisciplinary CNS precision medicine tumor board – teleconferenced with clinicians at multiple children's hospitals – which recommended adjuvant therapy with a fibroblast growth factor receptor (FGFR) inhibitor and/or a MAPK/ERK kinase (MEK) (where ERK is extracellular signal-regulated kinases) inhibitor, although she was not eligible for any clinical trials using these agents at that time. Therapy with the FGFR inhibitor ponatinib (off-study) is planned as a maintenance therapy upon clinical improvement.

3 | DISCUSSION

The prognosis for pediatric high-grade gliomas (HGGs) remains dismal despite multimodal treatment approaches, and the few reports on outcomes for spinal cord HGGs are also discouraging.[5,11,12] High-grade oligodendrogliomas in any location are uncommon in children and have unfavorable outcomes as well.[4,11,12] Only four AOs were confirmed among 250 HGG patients treated on the CCG-945 Children's Cancer Study Group clinical trial, and four patients with non-glioblastoma, non-anaplastic astrocytoma tumors among 107 patients with HGG treated on the ACNS0126 Children's Oncology Group trial.[11,12] Lundar et al. followed 35 children with cerebral oligodendrogliomas and found 5- and 10-year overall survival of only 27% and 18%, respectively, for the anaplastic tumors.[4] The prognosis of the very few

reported pediatric spinal AO is also poor; Merchant et al. reported two patients with AO among 11 high-grade pediatric spinal tumor patients who survived only 29 and 39 months, respectively.[5]

The molecular features of adult oligodendroglioma are well described. 1p/19q codeletion is found in 50–70% of adult gliomas and confers an improved response to chemotherapy and overall survival.[1,7] However, this high frequency and survival benefit for codeletion have not been shown in pediatric gliomas.[4,8,12,13] Similarly, methylation of the MGMT promoter and *IDH1* mutations are only rarely seen in pediatric HGG.[14] While these markers are helpful in guiding adult oligodendroglioma therapy, new molecular markers are needed for management of pediatric oligodendroglioma.

Molecular analysis of our patient's tumor displayed *NF1* loss-of-function mutations, *FGFR1*-activating mutations. Mutations in the tumor suppressor gene *NF1* are classically associated with NF1, a germline disorder characterized by neurofibromas, malignant peripheral nerve sheath tumors, optic pathway gliomas, and cutaneous findings.[15] *NF1* codes for neurofibromin, which promotes inactivation of Ras, downregulating the Ras-mitogen-activated protein kinase (Ras-MAPK) pathway.[16] Loss-of-function mutations in neurofibromin result in upregulation of the Ras-MAPK pathway and increased cellular proliferation. Sporadic, *NF1* somatic mutations have been observed by sequencing in many tumor types.[17] Interestingly, patients with a diagnosis of NF1 (germline *NF1* loss) have a slightly higher incidence of intramedullary spinal tumors.[18] This raises the question of whether glial precursor cells in the spine are predisposed to malignant transformation with *NF1* loss, whether somatic or germline.

The FGFR family is composed of five receptor tyrosine kinases that function in wound healing, angiogenesis, and cellular proliferation through their interaction with fibroblast growth factors.[19] FGFR1 interfaces with several pathway.[19] Sporadic *FGFR1* mutations have been observed in many tumor histologies, including two medulloblastoma, one low-grade glioma, and three glioblastoma cases.[17]

Given the lack of known effective therapies for the recurrent spinal AO in this child and the molecular leads to the oncogenesis of her tumor from the sequencing, targeted therapies are a consideration. In particular, inhibition of the Ras-MAPK pathway could be accomplished at the sites of both observed somatic mutations (Fig. 2). This could be done upstream via FGFR1 inhibition (e.g., ponatinib) or downstream via MEK inhibition (e.g., trametinib, which is actively being studied in other *NF1*-deficient tumors).[20]

Given that 64% of the sequenced tumor fraction expressed an *FGFR1* mutation and only 20% expressed alterations in *NF1*, we will initiate ponatinib for this patient. Ponatinib displays moderate CNS penetration and has published use in the pediatric population.[21] Future combination therapy with trametinib will be considered if the patient tolerates ponatinib therapy and does not display objective response. Response will be assessed by determining if the patient shows reduction in tumor size on surveillance brain imaging (a decrease of <25% of the largest diameters of measurable lesions and no evidence of new lesions) and remains without worsening tumor-related symptoms.

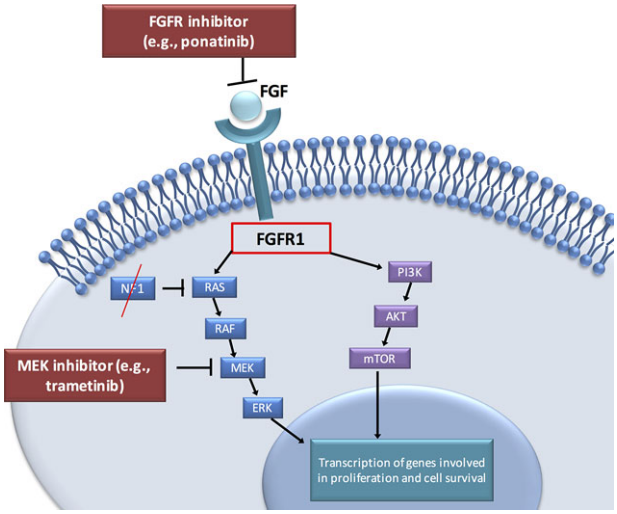

FIGURE 2 Proposed targeted inhibitors of the Ras-MAPK pathway. Neurofibromin loss-of-function and FGFR1 activation in this tumor are the two identified potential drivers of oncogenesis, and inhibitors of either pathway are attractive targeted therapy agents. Upstream inhibition of the Ras-MAPK pathway at the level of FGFR1 can be achieved with the tyrosine kinase inhibitor, ponatinib. Downstream inhibition of the Ras-MAPK pathway can be achieved with the MEK inhibitor, trametinib.

4 | CONCLUSION

We report genomic data for a case of pediatric spinal AO, a rare and aggressive tumor. The targetable mutations discovered in this child's tumor point to potential personalized therapies for her and suggest molecular drivers that may be involved in similar cases.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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