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LETTER TO THE EDITOR

Spinal Cord Pilocytic Astrocytoma With FGFR1-TACC1 Fusion and Anaplastic Transformation

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To the Editor:

Pilocytic astrocytoma (PA) is a WHO grade 1 primary neoplasm that accounts for ∼5.4% of all gliomas, occurs predominantly in childhood and adolescence, and usually arises in the cerebellum or cerebral midline structures (1, 2). The treatment of choice is surgical resection and the prognosis is excellent, with survival over 95% at 10 years (3). If a gross total resection (GTR) is achieved, postoperative radiation therapy or chemotherapy is not warranted, with low reported recurrence rates (4, 5). Development of anaplastic features is extremely uncommon, and many such tumors are associated with prior radiation therapy (6–8). However, little is known about the mechanisms and driver mutations associated with PA anaplasia (7).

The majority of sporadic PAs harbor alterations leading to MAPK/ERK pathway activation, which include aberrations affecting the *BRAF* gene. The most common abnormality (67%) is tandem duplication of 7q34, resulting in a transforming *KIAA1549-BRAF* fusion gene, in which *BRAF* lacks its auto-inhibitory domain and becomes constitutively active (9). However, the remaining 33% of PAs, although histologically similar, have less easily identifiable molecular aberrations. Other alterations that have been studied involve *FGFR1* receptor tyrosine kinase (RTK) gene and include hotspot point mutations, fusions, domain internal duplication and internal tandem duplication of the gene itself. While the *KIAA1549-BRAF* fusion is common in the cerebellum, *FGFR1* alterations are more common in extracerebellar midline structures (10). Interestingly, the *FGFR1-TACC1* fusion was recently described as the signature genetic alteration in a histologically defined subset of cerebellar PAs (11). We report the first case of a PA harboring the *FGFR1-TACC1* fusion in an uncommon spinal location, which recurred 15 months following surgical resection and exhibited anaplastic transformation.

CLINICAL CASE

A 22-year-old female patient presented with left shoulder numbness and weakness followed by left leg weakness and worsened gait. Cervical spine magnetic resonance imaging (MRI) with contrast demonstrated an enhancing intramedullary mass involving the brainstem and cervical spine, measuring 8.8 cm craniocaudally (Fig. 1A). A GTR was performed, no adjuvant therapy was provided, and the patient was observed. The mass was a histologically classic PA, a biphasic tumor comprised of loose oligodendroglioma-like areas in a myxoid and microcystic stroma with hyalinized blood vessels (Fig. 1C), with more solid areas containing densely fibrillar cellular arrangements with Rosenthal fibers (Fig. 1D, arrows). The immunohistochemical studies supported glial lineage with strong, diffuse positivity for GFAP (Fig. 1F). There was no detectable mitotic activity and no infiltration on H&E and neurofilament stains, while MIB-1 index was 0.5%. Although extraventricular neurocytoma was considered, the biphasic architecture, diffuse expression of GFAP (Fig. 1F) and absence of expression of the neural antigens Neu-N, chromogranin and neurofilament supported PA. A next-generation sequencing (NGS) panel detected a loss-of-function mutation (p.A2451fs) in the tumor suppressor *SETD2* and an *FGFR1-TACC1* fusion. FISH was negative for 1p/19q codeletion, effectively ruling out oligodendroglioma. Although the canonical *KIAA1549-BRAF* fusion and *V600E*

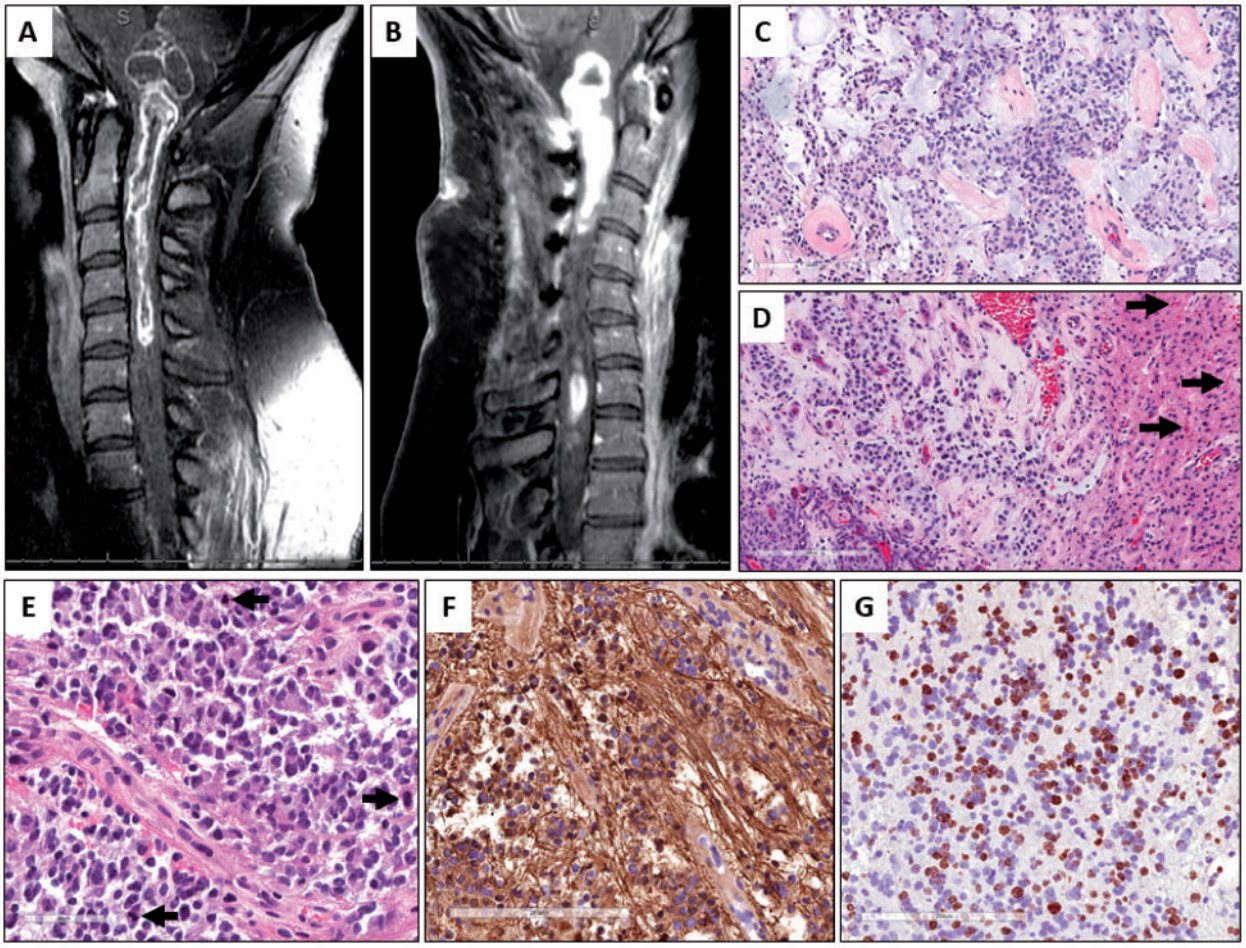

FIGURE 1. T1 post-contrast MRI of the spinal cord **(A, B)** and histological findings **(C–F)**. **(A)** Sagittal image of the primary tumor demonstrates a lobulated rim-enhancing mass, measuring 8.8 cm craniocaudal × 2.2 cm anteroposterior × 2.0 cm axial. Inferior margin of the mass contiguously extends to C5-6. **(B)** Sagittal image of the recurrent tumor demonstrates a homogeneously enhancing mass with a superior cystic component that extends to C7, measuring 5.9 cm craniocaudal × 1.8 cm anteroposterior × 2.2 cm axial. **(C, D)** H&E stain of the initial mass demonstrates a biphasic tumor with **(C)** loose oligodendroglial-like areas with variably hyalinized blood vessels, in a background of myxoid and microcystic stroma and more solid peripheral areas with densely fibrillar glial arrangements, microvascular proliferation **(D,** left lower corner**)** and Rosenthal fibers **(D**, arrows**)**. **(E)** H&E stain of the recurrent tumor shows frequent mitoses (up to 5/1 HPF, black arrows). **(F)** Glial fibrillary acidic protein IHC supports the glial nature of the recurrent tumor and highlights piloid processes and bipolar astrocytes. **(G)** MIB-1/Ki-67 immunohistochemical stain of recurrent tumor shows markedly increased activity.

mutation were absent, an increased *BRAF* gene copy number was identified, supporting the diagnosis of PA.

Due to her pregnancy, only noncontrast MRI studies were performed, thus delaying the detection of the tumor progression. Postcontrast MRI completed after delivery showed a recurrent, rapidly growing, enhancing mass, ultimately measuring 5.9 cm craniocaudally (Fig. 1B), with foci of abnormal enhancement below the level of the mass, concerning for drop metastases. Fifteen months after the initial surgery, she again underwent a GTR. Although the recurrent tumor was histologically similar to the original tumor, it no longer had Rosenthal fibers and also showed increased nuclear atypia, a dramatically increased mitotic index (up to 5 mitoses per 1 high-power field) (Fig. 1E), and a MIB-1 index of 25% (Fig. 1G), indicating malignant transformation. NGS on the recurrent specimen demonstrated the same genetic alterations and additionally, frequent copy number variations, consistent with chromosomal instability (Fig. 2). The patient received 6 weeks of craniospinal proton beam radiation therapy (PBRT) with concurrent temozolomide (TMZ) chemotherapy. She demonstrated clinical improvement after concurrent PBRT and TMZ. She is planned to receive monthly adjuvant TMZ for at least 12 cycles. If she progresses on TMZ, she will be treated with an *FGFR1-TACC1* inhibitor.

This is the first reported case of a spinal cord PA harboring an *FGFR1-TACC1* chromosomal fusion. Although this fusion was recently described as the signature genetic alteration in a subset of cerebellar PAs (11), no reports of this

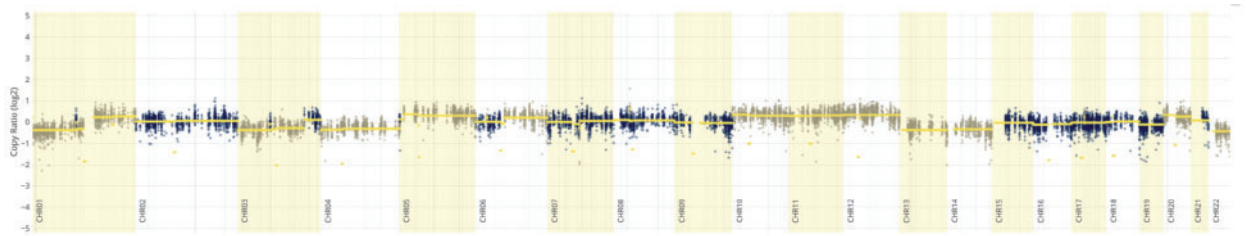

FIGURE 2. Copy number variations plot. Tumor demonstrates high aneuploidy, with frequent chromosomal gains and losses.

in the spinal cord have been made. The *FGFR-TACC* fusion proteins are constitutively active RTKs that induce chromosomal segregation defects, causing chromosomal instability, and trigger aneuploidy (12). Even though the recurrent tumor did in fact have frequent copy number variations, this has not been linked to anaplastic transformation in PAs. Another detected alteration was loss-of-function mutation in *SETD2* with 31% allele frequency. The *SETD2* gene encodes a histone-lysine methyltransferase, which regulates chromatin structure via H3K36 to influence gene transcription. Disruption of its enzymatic activity causes chromosomal volatility, abnormal gene regulation, and increased rate of spontaneous mutations (13). While *SETD2* mutation has been described in higher-grade gliomas, it was reported in only 3 PAs, but has not been specifically described to account for anaplastic transformation (13). Novel genes not covered by NGS or less well understood epigenetic factors may also be at play. Malignant transformations have been reported to occur postradiation (6, 8), but our patient did not receive any adjuvant treatment after the first GTR, therefore XRT was not a contributing factor. Glial tumor growth has been documented during pregnancy mostly in grade 2 or higher tumors (14). To date, there have only been 3 reports of PA progression during pregnancy, and none of those reported NGS data on their cases (15–17). The mechanism of this effect is not understood, and may be partly associated with progesterone, vascular endothelial growth factor, and placental growth factor elevations (14, 18). The ultimate cause for the malignant transformation remains uncertain and is likely multifactorial.

Because of the limited number of reported cases, the standard of care for anaplastic PAs has not been established, but treatment typically includes concurrent TMZ and standard XRT. More recently, PBRT has demonstrated volume reduction in progressive or inoperable PAs in 73% of patients (19). Even though our patient clinically improved after 6 weeks of concurrent PBRT and TMZ, the long-term outcomes of this regimen have not yet been determined. Clinical trials targeting the *FGFR* or the *SETD2* mutation may be additional treatment options in case of future recurrences. This case suggests that PAs with oligodendroglioma-like component occurring in the spinal cord, like their cerebellar counterparts, can harbor the *FGFR1-TACC1* fusion. Further studies are warranted to examine the role of *FGFR1-TACC1* fusions, *SETD2* mutations and chromosomal instability in anaplastic transformation of spinal cord PAs.

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