

Spinal high-grade astrocytoma with piloid features arising in a patient with molecularly confirmed cerebellar pilocytic astrocytoma

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Abstract

Pilocytic astrocytoma (PA) is a benign tumor with a low risk of high-grade transformation. High-grade astrocytoma with piloid features (HGAP) is a recently recognized tumor entity that may arise de novo or from low-grade gliomas. Here, we report a patient harboring both a fourth ventricular PA and a spinal cord tumor. Methylation profiling classified the brain tumor as PA and the spinal tumor as HGAP. Both tumors shared a *KIAA1549::BRAF* fusion with identical DNA breakpoints, confirming a common clonal origin. The spinal tumor also showed complex chromosome copy number aberrations, including homozygous deletion of *CDKN2A/B*. These findings suggest additional molecular alterations associated with tumor progression within the piloid lineage. To our knowledge, this is the first report providing comprehensive, paired molecular characterization of both PA and HGAP in the same patient, offering insight into their potential evolutionary relationship.

Pilocytic astrocytoma (PA) is a benign neuroepithelial tumor with a low propensity for malignant transformation, primarily driven by the *KIAA1549::BRAF* fusion.^{1,2} While PA is generally associated with a favorable prognosis, rare cases of malignant progression have been documented, often in the context of prior radiotherapy or chemotherapy.³ However, spontaneous malignant transformation in the absence of such treatments remains an exceedingly rare phenomenon. High-grade astrocytoma with piloid features (HGAP) is a recently defined tumor entity that may arise de novo or evolve from pre-existing low-grade gliomas, even in the absence of prior radiotherapy. HGAP is characterized by activation of the MAPK pathway and is frequently associated with additional genetic alterations, such as *CDKN2A/B* deletion or complex chromosomal copy number changes.^{4,5} The molecular mechanisms underlying the biological evolution of PA tumors are not yet fully elucidated, but they likely involve complex genetic and epigenetic alterations.

In this report, we report a patient with a fourth ventricular PA and a spinal cord tumor classified as HGAP by DNA methylation profiling. Integrated genomic and methylation analyses

confirmed a shared clonal origin between the two lesions and revealed distinct molecular alterations potentially associated with tumor progression within the piloid lineage.

Case Presentation

An 18-year-old female patient presented with a 1-month history of progressive back pain, numbness, and impaired mobility in both lower limbs. Retrospective inquiry additionally revealed intermittent early-morning headache and nausea over the preceding 18 months, which had been attributed to migraine or study-related stress and never prompted neuro-imaging apart from a non-contrast computed tomography (CT) that was reported as mild ventricular dilatation. Her maternal grandmother had cardia cancer, and her paternal aunt had ovarian cancer; no other family history of malignancy or neurofibromatosis was reported. The spinal tumor was therefore the first symptomatic lesion, whereas the fourth-ventricular mass was discovered incidentally when magnetic resonance imaging

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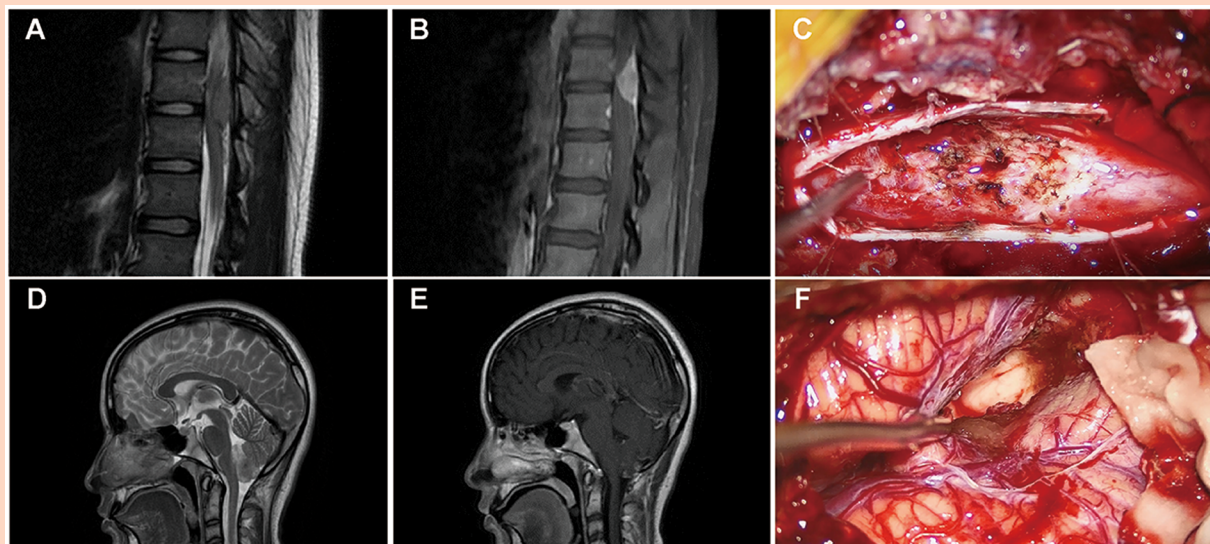


Figure 1. Imaging and Surgical Findings. (A and B) Thoracic MRI showing a 2.1 × 1.1 cm tumor in the T10-T11 segments, isointense on T1WI and slightly hyperintense on T2WI, with uniform enhancement after contrast. (C) Intraoperative findings showed the spinal cord tumor closely adhered to the spinal cord with unclear boundaries. (D-E) Brain MRI demonstrated a 3.5 × 2.0 cm mass in the fourth ventricle. The lesion was uniformly hypointense on T1WI and hyperintense on T2WI, with no significant enhancement at the upper edge but multiple nodular enhancements at the lower edge after contrast administration. (F) Intraoperative findings showed the fourth ventricle tumor attached to the lower part of the rhomboid fossa with relatively clear boundaries.

(MRI) of the entire neural axis was performed to rule out spinal cord compression. MRI revealed a 2.1 × 1.1 cm tumor in the T10-T11 spinal cord segments, isointense on T1WI and slightly hyperintense on T2WI, with uniform enhancement after contrast administration (Figure 1A and B). Additionally, a 3.5 × 2.0 cm mass was identified in the fourth ventricle, uniformly hypointense on T1WI and hyperintense on T2WI, with multiple nodular enhancements at the lower edge after contrast administration (Figure 1D and E). The patient underwent resection of the intraspinal lesion, followed by removal of the brain tumor 10 days later (Figure 1C and F).

Histopathology of the spinal cord tumor revealed hypercellularity, sheets of oval and spindle-shaped cells, a high nucleus-to-cytoplasm ratio, and numerous mitoses (>20 mitoses/10 HPF). Immunohistochemical staining showed positivity for S100, ATRX, SOX10, Olig2 (patchy), and H3 K27me3 (patchy), and negativity for GFAP, H3 K37M, and IDH1 R132, and a Ki-67 labeling index of over 20% (Figure S1A, D-F). The initial diagnosis was malignant peripheral nerve sheath tumor (MPNST). Histopathology of the brain tumor exhibited biphasic histological characteristics, with Rosenthal fibers present in both dense and loose areas (Figure S1B and C). Multipolar cells, eosinophilic bodies, and oligodendrocyte-like cells were observed. The tumor cells were positive for GFAP and ATRX, negative for IDH1 R132, and had a Ki67 index of <2%. The final diagnosis was PA, WHO grade 1.

Molecular analysis using a custom 638-gene pan-cancer panel DNA NGS revealed a *KIAA1549::BRAF* fusion with identical breakpoints in intron 15 of *KIAA1549* and intron 8 of *BRAF* in both tumors, indicating a common origin (Figure 2A). The brain tumor showed no additional genomic

alterations (Figure 2B), while the spinal cord tumor exhibited a complex genomic profile with multiple chromosomal losses and a single somatic point mutation (*PRKAR1A* c.1012T>G p. X338E) (Figure 2C). Tumor mutational burden was low in both tumors (<10 mutations/Mb), and neither showed evidence of microsatellite instability. Methylation-based classification using the DKFZ brain tumor classifier (v11b4) assigned the fourth ventricle tumor to “posterior fossa pilocytic astrocytoma (PAPF)” (calibrated score > 0.9) and the spinal cord tumor with “high-grade astrocytoma with piloid features (HGAP)” (calibrated score > 0.9) (Figure S2A). Copy number variation (CNV) analysis from this assay also revealed additional complex chromosomal alterations and a homozygous deletion of *CDKN2A/B* in the spinal cord tumor, consistent with findings from the 638-gene panel (Figure S2B and C). Germline DNA NGS analysis from peripheral blood showed no pathogenic or likely pathogenic variants in established cancer susceptibility genes, consistent with the absence of clinical features suggestive of a hereditary tumor syndrome.

The patient received radiotherapy for the spinal cord tumor, with a total dose of 46 Gy delivered in 2 Gy fractions. She was also treated with targeted therapy (trametinib 2 mg orally once daily and dabrafenib 150 mg orally twice daily for 1 month), which was later switched to temozolomide 100 mg orally once daily due to adverse effects. Additionally, the patient underwent rehabilitation treatment. Postoperatively, she experienced partial recovery of sensory and motor functions in both lower limbs and was able to walk with support. However, a recent MRI scan 10 months post-surgery revealed tumor spread in the spinal cord and pia mater, with the development of headaches and hydrocephalus.

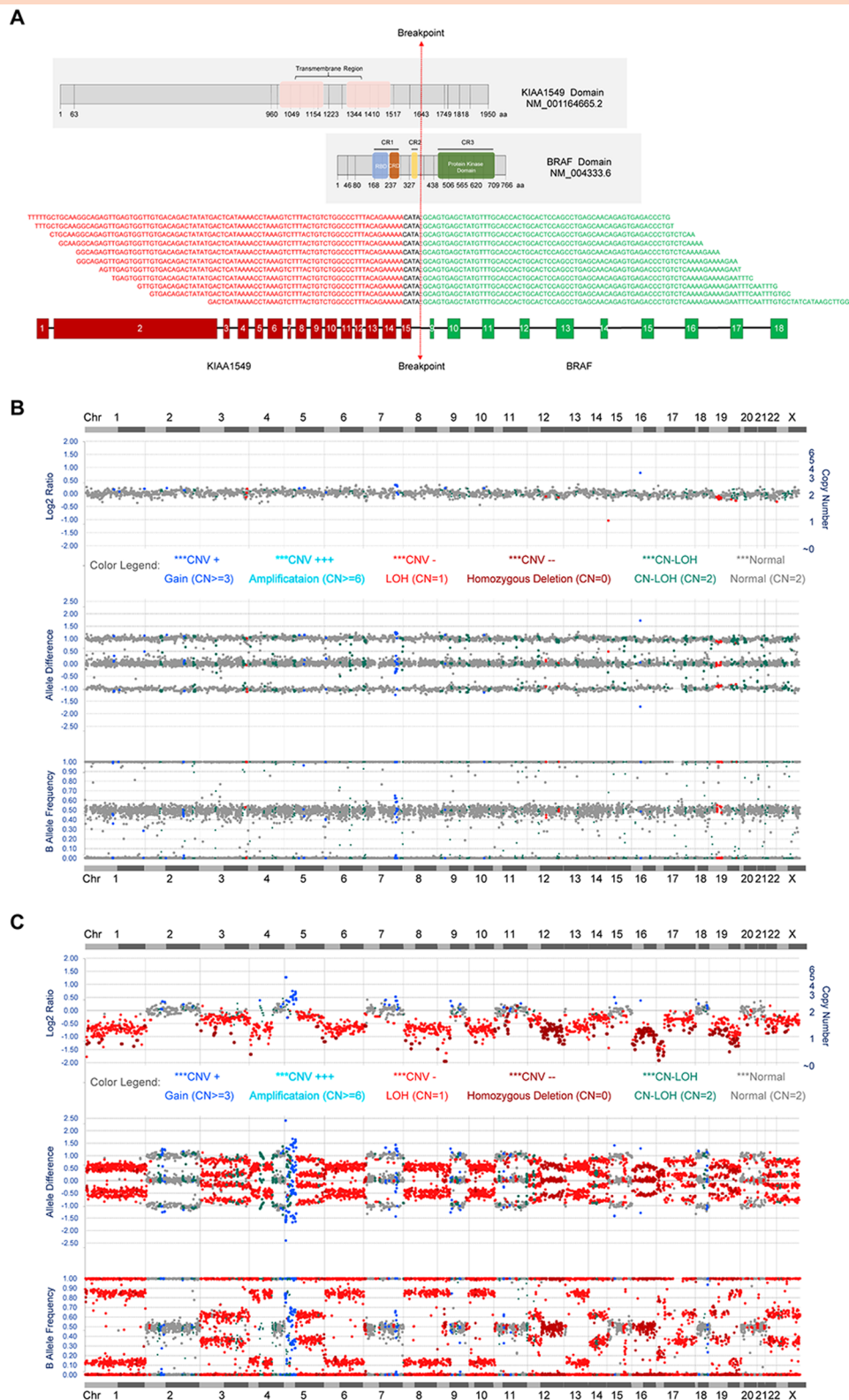


Figure 2. Molecular characterization of *KIAA1549:BRAF* fusion. (A) DNA next-generation sequencing (NGS) revealed a *KIAA1549:BRAF* fusion resulting from tandem duplication with identical breakpoints in intron 15 of *KIAA1549* and intron 8 of *BRAF* in both the spinal cord and brain tumors. (B) The brain tumor showed no additional genomic alterations. (C) The spinal cord tumor exhibited a complex genomic profile with multiple chromosomal losses and a single somatic point mutation (*PRKARIA* c.1012T>G p. X338E).

Discussion

Although PA is a low-grade tumor, rare cases of spinal or intraventricular spread, as well as spontaneous progression to a higher grade without prior radiotherapy, have been reported.^{6–9} In one such case, a patient developed malignant transformation and intracranial dissemination 17 months after initial surgery; however, molecular characterization was not performed.¹⁰ The biological relationship between PA and high-grade tumors remains incompletely understood. Here, we present a pediatric case in which a PA and a spatially distinct HGAP were both identified, and provide comprehensive molecular characterization, highlighting the complexity and potential heterogeneity of this tumor's progression.

Both tumors harbored an identical *KIAA1549::BRAF* fusion, a driver event present in approximately two-thirds of PA cases,^{11–13} confirming their shared clonal origin. However, the spinal HGAP acquired additional genomic alterations—most notably a homozygous deletion of *CDKN2A/B* and a complex profile of chromosomal losses—that were absent in the cerebellar PA. These findings suggest that the loss of tumor suppressor genes, such as *CDKN2A/B*, may have contributed to the rapid progression and malignant transformation of the tumor.^{14,15} The preservation of *ATRX* expression in this high-grade lesion further aligns with the molecular signature of HGAP, where approximately 50%–60% of cases retain the protein.^{4,5} Functionally, preserved *ATRX* suggests that malignant transformation may be driven by cell-cycle dysregulation, via *CDKN2A/B* loss, rather than the alternative lengthening of telomeres (ALT) pathway typical of *ATRX*-deficient diffuse gliomas.¹⁶ This molecular profile underscores a distinct evolutionary trajectory within the piloid lineage, achieving malignancy through cell-cycle dysregulation while maintaining stable telomere regulatory mechanisms.

The short symptomatic history of the spinal lesion (≈1 month) initially appears at odds with the indolent nature of WHO grade 1 PA. However, re-evaluation of prior imaging demonstrated at least 18 months of gradually progressive ventricular dilatation, implying that the fourth-ventricular PA had been present, and largely asymptomatic, for a considerable period. One possible interpretation is that tumor cells seeded to the spinal canal long before the spinal mass became biologically aggressive; the subsequent acquisition of *CDKN2A/B* homozygous deletion and catastrophic chromosomal losses then precipitated rapid malignant progression at the metastatic site. Alternatively, a higher-grade subclone may have already been present within the primary tumor and contributed to subsequent spread. While cerebrospinal fluid dissemination is a recognized mechanism in gliomas,¹⁷ direct evidence supporting a specific route of dissemination in this case is lacking; the precise timing and molecular triggers of progression, therefore, remain speculative.

Future research should focus on elucidating the molecular pathways involved in the evolution of tumors within the piloid astrocytic lineage, particularly the mechanisms driving progression from low-grade PA to HGAP. Understanding the role of tumor suppressor genes, such as *CDKN2A/B*, and the interplay between the MAPK and PI3K/AKT pathways may provide new therapeutic targets. Additionally, longitudinal studies of PA patients with and without malignant

transformation could help identify early biomarkers of progression.

We acknowledge several limitations of this study. First, the current 10-month follow-up is insufficient to capture the full natural history of the disease. Second, sampling of the primary tumor did not distinguish between radiologically distinct regions, and the possibility of intratumoral heterogeneity cannot be excluded. Third, biopsy material from the spinal lesion was limited; therefore, quantification of piloid areas and comprehensive ultrastructural studies were not feasible.

In conclusion, we report a rare case of a spinal high-grade astrocytoma with piloid features arising in a patient with a molecularly confirmed cerebellar pilocytic astrocytoma. Integrated molecular analyses demonstrated a shared clonal origin, supported by an identical *KIAA1549::BRAF* fusion, while additional alterations in the spinal tumor, including *CDKN2A/B* homozygous deletion and complex chromosomal changes, suggest progression within the piloid astrocytic lineage. This case highlights the importance of molecular diagnostics in understanding PA progression and underscores the need for further research to improve outcomes for patients with this challenging disease.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Advances* (<https://academic.oup.com/noa>).

Keywords

high-grade astrocytoma with piloid features | *KIAA1549::BRAF* fusion | methylation profiling | pilocytic astrocytoma | tumor evolution

Author Contributions

Yulun Huang did the conception; Xiaoci Rong, Haiping Zhu, Xuetao Li, Jie Shao did data curation and analysis; Nan Chen, Sujuan Zhou, Yanghao Hou and Yun Ning did the validation; Xiaoci Rong, Dongbing Li, Wenjuan Gan, and Xiaohong Yao did writing-original draft; All authors did writing-review and editing.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethics Statement and Patient Consent

The participant provided written informed consent before inclusion in the study. The study was conducted in accordance with the Declaration of Helsinki.

Consent to Publish

Not applicable.

Data Availability

The data and materials of this study will be available from the corresponding author (Yulun Huang) upon reasonable request.

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