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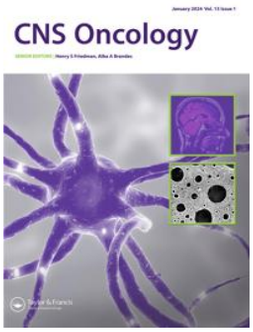

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CASE REPORT

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Diffuse pediatric-type high grade glioma, RTK1 subtype, subclass C with *SYN2*::*PPARG* fusion in an older adult

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ABSTRACT

Diffuse pediatric-type high-grade glioma (pHGG), RTK1 subtype, is an uncommon aggressive tumor affecting both children and adults. We describe the case of a 66-year-old woman who presented with a left frontal lobe mass. Following surgical resection, the patient developed herpes simplex virus 2 meningoencephalitis, resulting in death. Histological examination revealed a high-grade glioma demonstrating nuclear pleomorphism, high mitotic activity, vascular proliferation and necrosis. The tumor also exhibited oligodendroglial-like features, nuclear clusters and small true rosette-like structures. Genetic analysis identified partial arm 1p loss and 19q loss, *PDGFRA*, *MYCN* and *MDM4* amplification, an *ATRX* mutation and a novel *SYN2*::*PPARG* fusion. Homozygous *CDKN2A/B* deletion was also present. Genomic DNA methylation profiling matched diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C. This case underscores the importance of utilizing advanced molecular and genomic techniques for accurately diagnosing glial tumors. Further study of the *SYN2*::*PPARG* fusion in gliomas could potentially offer insights into its role in glioma biology and possibly help elucidate therapeutic strategies for tumors with *PPARG* fusions.

ARTICLE HIGHLIGHTS

- We report a case of diffuse pediatric-type high-grade glioma (pHGG), RTK1 subtype, subclass C in an adult confirmed by genomic DNA methylation analysis.
- The tumor demonstrated *PDGFRA*, *MYCN* and *MDM4* amplification, and *ATRX and KIT* pathogenic mutations.
- The tumor also harbored a *SYN2*::*PPARG* gene fusion not previously reported in glioma.
- The case illustrates the importance of integrating advanced molecular techniques into the diagnostic process for older patients with atypical presentations of high-grade glioma.
- The potential biological significance and possible future therapeutic implications of the *SYN2*::*PPARG* gene fusion are discussed.

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Diffuse pediatric-type high-grade glioma; RTK1 subtype; subclass C; *SYN2*::*PPARG* gene fusion; *PDGFRA* amplification; *MYCN* amplification; *MDM4* amplification; *ATRX* mutation; genomic DNA methylation analysis

1. Introduction

Diffuse pediatric-type high-grade gliomas (pHGG) are aggressive central nervous system tumors seen in children, but also in young and older adults, reportedly from 8 to up to 71 years of age [1]. The World Health Organization (WHO) recently classified these tumors based on distinct genetic and molecular profiles, distinguishing between other histone H3 gene and *IDH1/2* gene wildtype variants of high-grade diffuse glioma [1–3].

PPARG encodes the peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor vital for regulating metabolism and adipocyte and immune function, and is implicated in carcinogenesis. *PPARG* has been identified as a fusion partner in various cancers, indicating its broader potential impact on tumor development [4–6]. *SYN2* encodes synapsin II, a neuronal protein involved in neurotransmitter regulation and synapse formation. Although primarily associated with neural signaling, recent studies have linked *SYN2* to fusion genes in cancers.

This report describes a case of a 66-year-old woman with a diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C harboring a *SYN2*::*PPARG* fusion.

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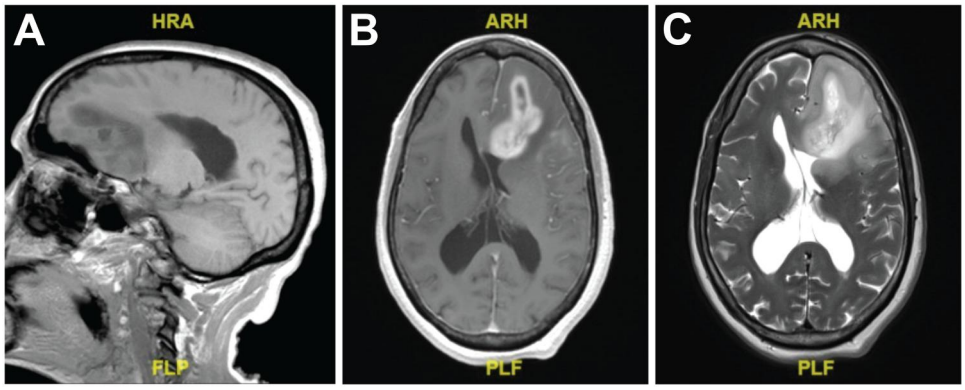

Figure 1. Magnetic resonance imaging of the tumor. (A) Sagittal T1-weighted image demonstrating the left frontal tumor. (B) Axial post-contrast T1-weighted image showing tumor contrast enhancement, mass effect and a left to right midline shift. (C) Axial T2-weighted image demonstrating peritumoral and edema and midline shift.

Detection of this fusion in a pediatric-type high-grade glioma in an older patient highlights the importance of molecular profiling in gliomas of patients of all ages and may contribute to the future understanding of the biology of variants of these tumors.

1.1. Clinical history

A 66-year-old female with a noncontributory medical history presented to the emergency department after exhibiting several months of progressive forgetfulness and cognitive decline. Magnetic resonance imaging (MRI) revealed a 6.7 by 4.8 cm complex left frontal contrast enhancing mass demonstrating prominent vasculature and vasogenic edema causing a left to right midline shift (Figure 1).

The patient was admitted to the neurological ICU, intubated, and placed on dexamethasone and continuous EEG monitoring, with anti-epileptic drugs as needed. She underwent a craniotomy and resection of the mass. Post-operative imaging demonstrated persistent enhancement in the left frontal lobe, consistent with residual neoplasm. She temporarily improved before developing fever and acute mental status changes 9 days after surgery. The patient was re-intubated, placed on broad spectrum antibiotics, and a lumbar puncture was performed. She then developed left hemispheric status epilepticus and was medically sedated. The CSF was positive for herpes simplex virus 2 (HSV-2) by polymerase chain reaction (PCR). She was diagnosed with HSV-2 meningoencephalitis and was placed on IV acyclovir. She then experienced another episode of clinical and electrographic seizures. Given the poor prognosis, the family decided upon extubation with comfort care and the patient expired approximately 3 weeks after surgery.

1.2. Histology

H&E sections demonstrated a hypercellular glial neoplasm with moderate nuclear hyperchromasia and pleomorphism, and focal areas showing oligodendroglial-like differentiation (Figure 2A-D). Endothelial hypertrophy was prominent. Vascular proliferation, albeit, less frequent, was also present (Figure 2C). A perivascular growth pattern was noted in some areas, whereas sheet-like growth was present in others. Occasional nuclear clusters, sometimes resembling multinucleated cells, and small true rosette-like structures were noted (Figure 2B and 2D). The background appeared myxoid in some areas. Apoptotic bodies were abundant and up to nine mitotic figures were counted in ten 400x fields. Both palisading and sheet necrosis were present. Immunohistochemistry further revealed that the Ki-67 labeling index was up to approximately 85% (Figure 2E). The tumor was diffusely positive for GFAP and Olig2 proteins (Figure 2F and 2G) and negative for p53 (not shown). Synaptophysin showed focal positivity and ATRX was mostly negative, although a small subset of cells retained expression (Figure 2H and 2I).

1.3. Molecular testing

Fluorescence *in situ* hybridization (FISH) demonstrated polysomy of chromosomal region 1q25, with loss of 1p36 and 19q13. One copy of the *CDKN2A/B* locus (9p21.3) was lost in 10% of the tumor nuclei examined, and both signals were lost in 82% of the tumor nuclei examined. *MGMT* promoter hypermethylation was detected by pyrosequencing. NGS (PGDx elio^{TM} tissue complete 505 gene panel, Labcorp) revealed *KIT* p.H697Y (c.2089C > T, variant allele frequency 0.911) and *ATRX* p.F2113Sfs*9 (c.6338_6341delTTAT, variant allele frequency 0.446) pathogenic mutations.

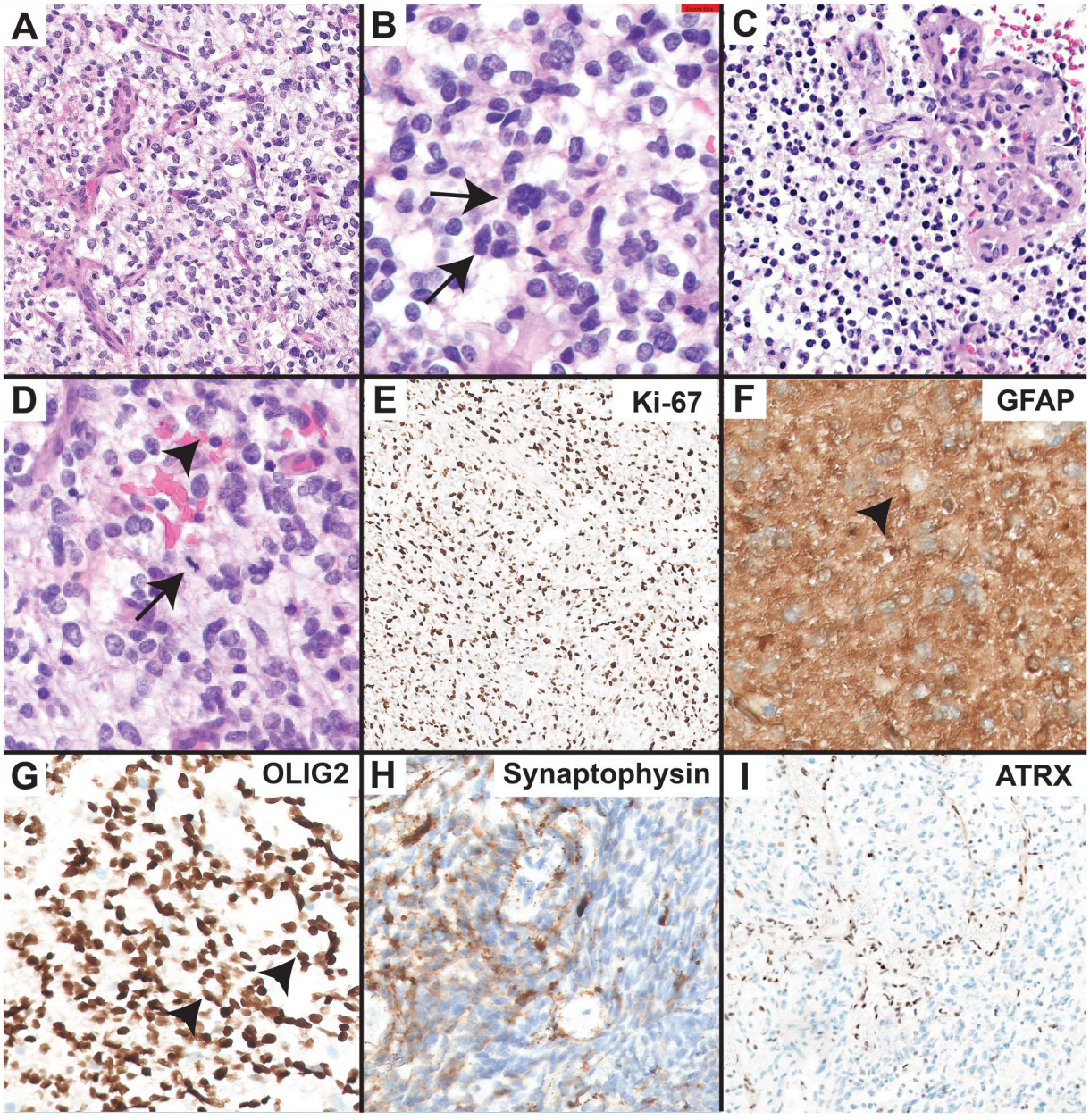

Figure 2. Histologic features of the tumor. (A) Low magnification view of the hypercellular and pleomorphic tumor demonstrating oligodendroglial-like cytomorphology (H&E). (B-D) Higher magnification views of the tumor (H&E). Arrows in (B) indicate nuclear clusters. Microvascular proliferation was evident (C). In (D) the arrow points out mitotic activity and the arrowhead identifies a true rosette-like structure. (E) Ki-67 immunostaining was high. (F-G) The tumor was diffusely immunoreactive for GFAP and Olig2. Arrowheads in both panels depict true rosette-like structures. (H) Synaptophysin was focally positive. (I) ATRX was mostly negative. ATRX immunoreactive tumor capillaries were present representing an internal positive control.

Targeted RNAseq (Archer FUSIONPlex, Integrated DNA Technologies) revealed an in-frame *SYN2*::*PPARG* fusion (15 unique sequence reads) between *SYN2* exon 12 and *PPARG* intron 1 (Figure 3A). *SYN2* and *PPARG* are adjacent genes located at chromosomal segment 3p.25.2.

Genomic DNA methylation analysis of the tumor utilizing the Illumina MethylationEPIC platform [7] yielded a diagnostic match to diffuse pediatric-type high grade glioma, RTK1 subtype, subclass C. Confidence scores were 0.78 and 0.81 using the Heidelberg classifier versions 11b6 and 12b6, and the NCI/Bethesda classifier, respectively [7,8]. Dimensionality reduction via Uniform Manifold Approximation and Projection (UMAP) confirmed the methylation classification (Figure 3B). This analysis also confirmed *MGMT* promoter hypermethylation and deep deletion of *CDKN2A/B*. It additionally revealed a

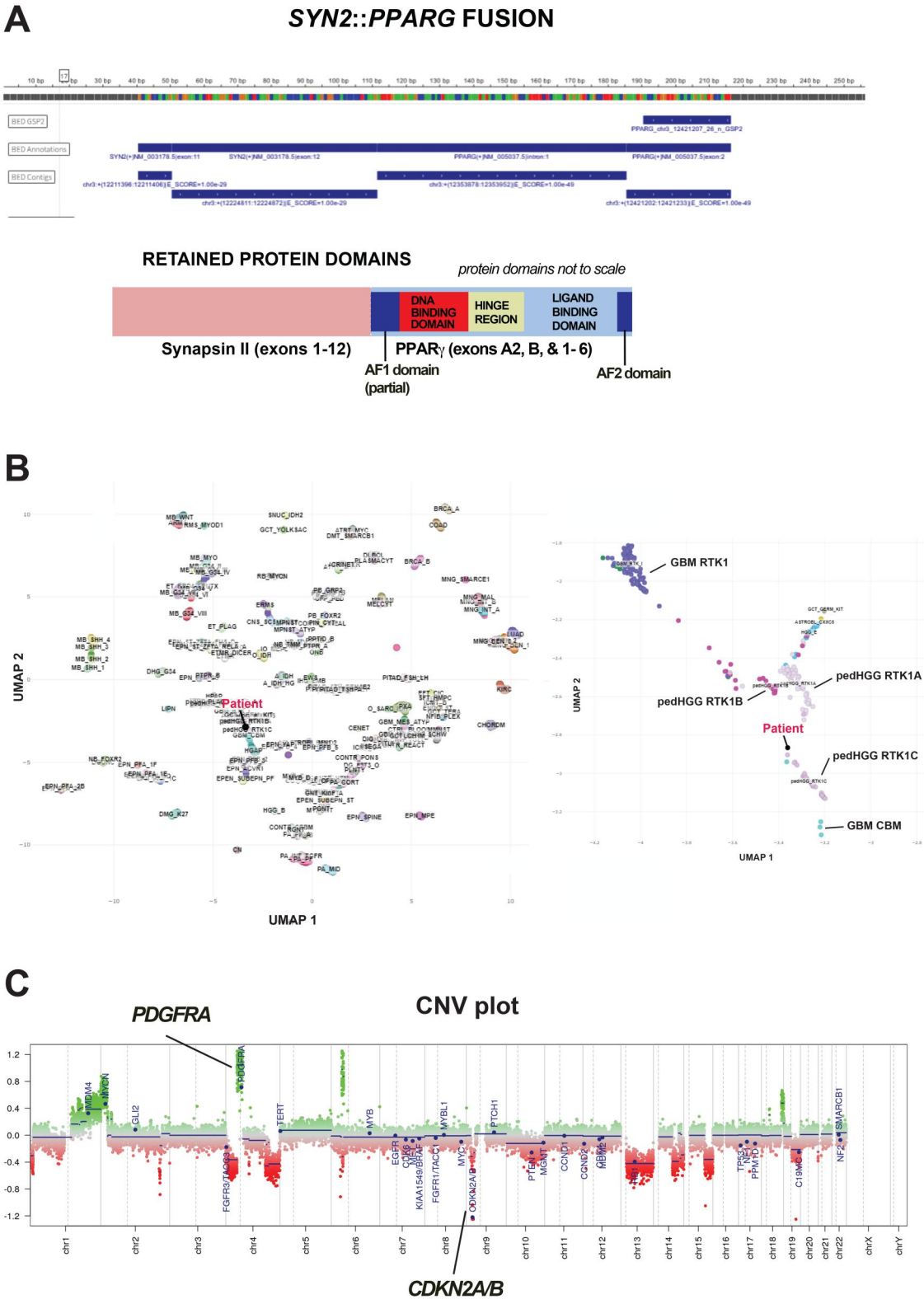

Figure 3. Gene fusion, Methylation UMAP analysis and CNV analysis. (A) Cartoon depicting *SYN2::PPARG* fusion. Fusion was between exon 12 of *SYN2* and intron 1 of *PPARG*. (B) UMAP analysis clustering of the patient's tumor DNA methylation data. An enlarged portion of the UMAP showing tumor clustering with diffuse pediatric glioma, RTK1 subtype, subclass C is depicted on the right. (C) CNV plot. *PDGFRA* amplification and *CDKN2A/B* deletion are indicated.

complex chromosomal copy number variation (CNV) pattern including partial arm 1p and whole arm 19q loss. It also showed 1q gain, partial 2q, 4p, partial 4q, partial 6p, partial 9p, partial 10p, 13q, partial 14q, and partial 15q loss, as well as *PDGFRA*, *MYCN* and *MDM4* amplification (Figure 3C).

2. Discussion

The diagnosis of diffuse pediatric-type high-grade glioma (pHGG), RTK1 subtype carries a CNS WHO grade of 4 and is defined by absence of *H3F3A* and *IDH1/2* gene mutations, a genomic DNA methylation profile compatible with a known pHGG subtype (RTK1, RTK2 or *MYCN*) or other characteristic molecular alterations, as well as histologic features of malignancy, i.e., increased mitotic activity, microvascular proliferation and/or necrosis [2,3,7]. RTK1 subtypes most often harbor *PDGFA* alterations and RTK2 subtypes frequently have activating *EGFR* alterations. Methylation analysis further stratifies the RTK1 subtype into three subclasses, A-C.

Some pediatric high-grade gliomas harbor histone 3 gene mutations (most often in *H3F3A*), e.g., diffuse midline glioma (H3 K27-mutant) and diffuse hemispheric glioma (H3 G34-mutant), while *IDH1/2* mutations are rare. The remaining H3 gene and *IDH* gene wildtype high-grade pediatric glial tumors include glioblastoma, anaplastic pleomorphic xanthoastrocytoma, infant-type hemispheric glioma, and others. These tumors exhibit substantial genomic and epigenetic diversity and are associated with different clinical outcomes and potential therapeutic responses [3].

They are defined by characteristic molecular alterations and sometimes may also require methylation analysis for a definitive diagnosis [9].

In adult type diffuse gliomas, astrocytoma, IDH-mutant and oligodendroglioma are partially defined by *IDH1/2* mutations. Oligodendroglioma is further defined by the presence of chromosome 1p and 19q hemizygous codeletion. This case of diffuse pediatric-type high-grade glioma showed partial arm 1p loss and 19q loss, which along with its oligodendroglioma-like cytomorphology represents a diagnostic pitfall for these and other oligodendroglial-like tumors. This makes accurate determination of 1p and 19q status essential. Because the tumor exhibited oligodendroglial-like features, nuclear clusters and true rosette-like structures, similar to diffuse glioneuronal tumors [9], it highlights the potential presence of common histologic features between these molecularly distinct tumors.

The RTK1 subtype of diffuse pediatric-type high-grade glioma most often occurs in the supratentorial brain (82% of cases) and less commonly at infratentorial/brainstem sites (18% of cases) [3]. Cases of this subtype have also been reported in the setting of germline mismatch repair aberration and radiation therapy [10].

A recent study reported 3 cases of pediatric high-grade glioma with *PDGFRA* amplification in somewhat younger adults with Li-Fraumeni syndrome [11]. None had *ATRX* mutations. *ATRX* mutation is known to result in genomic instability and cellular multinucleation [12,13], which may account for the complex CNV pattern and nuclear clusters/multinucleate cells observed in this case.

Synapsin II is a synaptic vesicle phosphoprotein that modulates synaptic transmission by interacting with presynaptic Ca^{2+} channels and promoting asynchronous GABA (γ-aminobutyric acid) release [14]. PPARγ is a nuclear receptor that promotes adipogenesis and is involved in regulating gene expression and the function of adipocytes and immune cells [15]. *PPARG* is the downstream component of the observed gene fusion and the fusion contains exons A2, B and 1–6 of the *PPARG* gene encompassing all translated exons (exons 1–6) common to both major PPARγ protein isoforms (PPARγ1 and PPARγ2), including their DNA and ligand binding functional domains (Figure 3A) [15]. *PPARG* is therefore likely functionally overexpressed as a consequence of the fusion. The fusion additionally contains all exons encoding PPARγ2 (B and 1–6). Evidence suggests that PPARγ may function as a tumor suppressor or oncogenic molecule depending on the type of cancer. Activation of the PPARγ/retinoid X receptor alpha pathway leads to tumor suppression in several cancers, including colon, lung, pancreatic, prostate, and breast cancers [14]. In agreement with this evidence, are reports of *PPARG* loss-of-function mutations in digestive tract cancers, including S317C, R316H, Q314P, K347X, and K450Q [11]. Interestingly, bladder cancer cases have demonstrated both loss-of-function (S74C, F310S, E455Q, H494Y) and gain-of-function (E3K, P113S, R168K, R164W, S249L, M280I, I290M, T475M) *PPARG* mutations.

PPARG::SYN2 gene fusions have been previously reported in a case of small cell lung cancer [4], a sinonasal adenocarcinoma [5] and a salivary gland acinic cell carcinoma [6]. This appears to be the first instance of the *PPARG::SYN2* fusion reported in diffuse pediatric-type high-grade glioma. Molecular characterization of larger series of these tumors is needed to determine the frequency of this potential genetic driver gene fusion in these tumors and whether the *SYN2::PPARG* fusion is of diagnostic or prognostic significance. Such studies might potentially lead to the development of targeted treatment strategies for tumors harboring this gene fusion. For instance, PPARγ activity may be pharmacologically modulated through its ligand binding domain [15] and recent

evidence suggests that it may be also modulated by genetic targeting of its AF-1 domain (exons A1, A2 and B) [16]. The latter is a ligand-independent transactivation domain that regulates alternate splicing and therefore the specificity of PPARγ isoform transcriptional activity. Perhaps analogous strategies could be developed to enhance possible tumor suppressor or antagonize potential tumor promotor effects of *PPARG* fusions.

A limitation of this case is that the patient developed a fatal HSV-2 meningoencephalitis shortly after surgery precluding evaluation of the post-surgical clinical aggressiveness of the tumor. Nevertheless, the case underscores the utility of gene fusion detection and of genomic DNA methylation analysis in the subtyping of glial tumors in order to optimize their diagnosis, prognostication and potential treatment in some cases. In particular, the case illustrates the importance of integrating advanced molecular techniques into the diagnostic process for older patients with atypical presentations of high-grade glioma, rather that hastily categorizing them as glioblastoma.

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Ethics statement

Written informed consent for publication of the patient's details was obtained from the patient's next of kin.

Author contributions

Mikaela Brentlinger: Writing - Original Draft and Review & Editing, Investigation, Formal Analysis. Jemini Patel: Writing - Original Draft. Ahmed Khan: Writing - Figure Legends. Eduardo Castro-Echeverry: Methodology, Formal Analysis. Zied Abdullaev: Methodology, Investigation, Formal Analysis, Data Curation, Writing - Editing. Kenneth Aldape: Investigation, Resources. Norman Lehman: Conceptualization, Study Design, Investigation, Formal Analysis, Supervision, Writing – Review & Editing.

Disclosure statement

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