

Radiation-Induced High-Grade Glioma in a Long-Term Survivor of Medulloblastoma: A Case Report

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Case Report

Keywords:

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10942986/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Advances in multimodal therapy have significantly improved survival in medulloblastoma, but long-term survivors remain at risk of secondary malignancies. We describe a rare case of radiation-induced high-grade glioma developing after a disease-free interval of approximately seven years, and nearly nine years following initial treatment.

Case Presentation

A 19-year-old male with a history of classical medulloblastoma (CNS WHO grade 4) presented nine years after his initial diagnosis with worsening headaches and fatigue. His primary tumor was treated with multiple surgical resections followed by high-dose craniospinal irradiation and adjuvant chemotherapy, after which he remained under surveillance. Seven years after completing treatment, he came in with a four-week history of weight loss and fatigue. One week before admission, he developed drowsiness, followed by a 10-day history of right focal seizures and increasing right-sided weakness. On neurological examination, he was obtunded with a Glasgow Coma Scale score of 9/15 and showed right-sided spastic hemiparesis with impaired verbal responsiveness.

Magnetic resonance imaging revealed multiple supratentorial lesions associated with extensive vasogenic edema and mild midline shift, raising concern for a secondary malignant neoplasm. A left frontal burr-hole biopsy was subsequently performed. Histopathological examination demonstrated a highly cellular glial neoplasm composed of pleomorphic, hyperchromatic tumor cells embedded within a fibrillary background. Prominent microvascular proliferation and frequent mitotic activity were identified, consistent with a high-grade infiltrating glioma. Immunohistochemical analysis showed diffuse glial fibrillary acidic protein (GFAP) positivity, absence of IDH1 R132H expression, retained ATRX nuclear staining, and a Ki-67 proliferation index of 15–20%. Tumor cells were negative for H3K27M, and mismatch repair protein expression was preserved. Based on the histopathological and immunophenotypic findings, a diagnosis of high-grade glioma, favoring astrocytoma, NOS, CNS WHO grade 4, was established.

Given the patient's previous exposure to craniospinal radiotherapy and the prolonged latency period of nine years between treatment of the primary medulloblastoma and development of the high grade glioma, the lesion was highly suggestive of radiation-induced high-grade glioma. Despite supportive management, the patient's clinical condition deteriorated rapidly, and he succumbed to the disease one month after diagnosis.

Conclusion

This case illustrates the development of a secondary high-grade glioma in a long-term survivor of medulloblastoma, most likely representing a radiation-induced malignancy. It highlights the critical importance of lifelong surveillance in survivors of pediatric brain tumors, as early detection of secondary

central nervous system neoplasms may allow timely intervention. Despite the limited therapeutic options available for these aggressive tumors, prompt recognition remains essential to optimize patient management and outcomes.

Introduction

Medulloblastoma is the most common malignant pediatric brain tumor, accounting for approximately 20% of childhood central nervous system (CNS) neoplasms. Standard therapy consists of maximal safe surgical resection followed by craniospinal irradiation and adjuvant chemotherapy. Advances in these multimodal treatment strategies have significantly improved survival, with five-year survival rates now exceeding 70% in many patient cohorts (1, 2).

Despite these improvements, long-term survivors remain at risk for late treatment-related complications, including endocrine dysfunction, neurocognitive impairment, and secondary malignant neoplasms. Radiation-induced tumors are a well-recognized consequence of cranial irradiation, with secondary gliomas representing one of the most aggressive and clinically challenging entities (1, 3).

Secondary high-grade gliomas typically develop several years after radiotherapy, often within previously irradiated regions, and are characterized by aggressive clinical behavior and poor prognosis (4). Importantly, these tumors may demonstrate molecular features distinct from those of primary gliomas, reflecting their unique pathogenesis.

We report the case of an adolescent patient who developed multifocal supratentorial high-grade glioma nine years after treatment for medulloblastoma, highlighting the long latency and aggressive nature of radiation-induced gliomas and emphasizing the need for vigilant long-term surveillance in survivors of pediatric brain malignancies.

Case Summary

A 19-year-old male, a known case of classical medulloblastoma (CNS WHO grade 4), presented with a 1-month history of weight loss and one-week history of progressive drowsiness. This was followed by a 10-day history of right-sided focal seizures and progressive right-sided weakness.

He was initially diagnosed in January 2016, when he underwent his first surgery (29/01/2016): suboccipital craniotomy with gross total resection. Postoperative MRI confirmed complete resection; however, MRI of the whole spine with contrast demonstrated leptomeningeal enhancement from T10–L1. Histopathology was consistent with classical medulloblastoma (WHO grade 4). The patient was subsequently lost to follow-up.

He re-presented in May 2016 with headaches and vomiting, there was radiological evidence of recurrence on CT brain (30/05/2016), for which he underwent a second surgery (02/06/2016): redo suboccipital craniotomy with maximal safe resection. Postoperative MRI demonstrated residual disease.

Due to hydrocephalus, a third procedure (11/06/2016) was performed with ventriculoperitoneal (VP) shunt insertion. Repeat histopathology revealed medulloblastoma with focal anaplasia (WHO grade 4).

He subsequently received multimodal therapy, including craniospinal irradiation (36 Gy with posterior fossa boost to a cumulative dose of 55.8 Gy) followed by combination chemotherapy with cisplatin, vincristine, and cyclophosphamide (High-risk ACNS0332 protocol), completing six cycles by March 2017.

Serial surveillance imaging from October 2016 through June 2018, including MRI brain and whole spine, consistently demonstrated no residual or recurrent disease and no evidence of drop metastases. In September 2017, he underwent VP shunt removal due to infection. His course was further complicated by tuberculous meningitis, for which he completed six months of anti-tuberculous therapy.

He remained in radiological remission on surveillance imaging until. On 25th February 2026, he developed seizures and weakness. MRI Brain with contrast revealed multiple intra-axial supratentorial and infratentorial lesions. MRI of the whole spine and cerebrospinal fluid cytology showed no evidence of leptomeningeal dissemination. Given the atypical pattern for medulloblastoma recurrence, a left frontal craniotomy and biopsy (05/03/2026) was performed.

Histopathological examination revealed a high-grade glial neoplasm composed of pleomorphic, hyperchromatic tumor cells in a fibrillary background, with microvascular proliferation and increased mitotic activity. Immunohistochemistry demonstrated GFAP positivity, IDH-1 wild-type status, intact ATRX expression, and a Ki-67 proliferation index of 15–20%. H3K27M was negative, and mismatch repair proteins were intact. The immunohistochemical profile is summarized in Table 1. These findings were consistent with a diagnosis of high-grade glioma, favoring astrocytoma, NOS, CNS WHO grade 4.

Table 1
Care Timeline

Date/Period	Clinical event
Jan 2016	Initial diagnosis of classical medulloblastoma; gross total resection
May–Jun 2016	Recurrence; second surgery and VP shunt insertion
2016–2017	Craniospinal irradiation with posterior fossa boost and six cycles of chemotherapy
2017–2018	Surveillance imaging showed no residual/recurrent disease
2018–2025	Continued disease-free interval
Feb 2026	New seizures and right-sided weakness; MRI showed multiple intracranial lesions
Mar 2026	Left frontal craniotomy and biopsy
Mar 2026	Diagnosis of high-grade glioma, favoring astrocytoma, NOS, CNS WHO grade 4
Mar–Apr 2026	Rapid neurological deterioration
Apr 2026	Death approximately one month after diagnosis

Table 2
Immunohistochemical profile

Marker	Result
GFAP	Positive
IDH-1	Negative
p53	Wild type expression
ATRX	Intact nuclear expression
Ki-67	Raised ($\approx 15\text{--}20\%$)
H3K27me3	Intact nuclear staining
H3K27M	Negative
MSH-2	Intact nuclear expression
MSH-6	Intact nuclear expression
MLH-1	Intact nuclear expression
PMS-2	Intact nuclear expression

The multifocal supratentorial distribution and absence of leptomeningeal disease were atypical for medulloblastoma recurrence, raising strong suspicion for a secondary malignancy. Despite supportive management and multidisciplinary care, the patient's neurological status continued to deteriorate, and he subsequently succumbed to the disease within one month of diagnosis.

Discussion

Radiation-induced gliomas RIGs occur in approximately 0.5–3% of pediatric brain tumor survivors, typically after a latency of 5–15 years. Our patients' presentation nearly a decade post-treatment underscores the long-term risks of craniospinal irradiation (3, 4).

The pathogenesis of RIG is multifactorial and extends beyond direct radiation-induced DNA damage. Ionizing radiation induces double-strand DNA breaks, oxidative stress, mitochondrial dysfunction, and persistent genomic instability that may persist for years after exposure. These processes promote the accumulation of somatic mutations, chromosomal rearrangements, telomere dysfunction, and epigenetic alterations that impair normal cell-cycle regulation and DNA repair mechanisms (3, 5, 6). Radiation also alters the tumor microenvironment through chronic neuroinflammation, microglial activation, vascular injury, and cytokine-mediated signaling, creating a pro-oncogenic environment that facilitates the malignant transformation of neural stem cells and glial precursor cells (1, 5). In addition, misrepair of radiation-induced DNA damage through error-prone non-homologous end joining contributes to chromosomal rearrangements, copy-number alterations, and persistent genomic instability, promoting clonal evolution of transformed glial precursor cells (5, 6). Individual susceptibility

may further be modified by inherited defects in DNA repair pathways, including TP53, ATM, and other cancer predisposition genes, although most RIGs arise sporadically (1, 5).

Recent molecular studies have demonstrated that RIGs are biologically distinct from de novo pediatric high-grade gliomas. They are characterized by recurrent copy-number alterations, including PDGFRA amplification, CDKN2A/B deletion, TP53 alterations, CDK4 amplification, and chromosomal abnormalities such as 1p loss and 1q gain, while typically lacking IDH1/2 mutations, H3 K27M, and H3 G34 alterations (6, 7). Genomic profiling by Deng et al. and DeSisto et al. further confirmed that most RIGs cluster within the pediatric receptor tyrosine kinase (RTK-I) methylation subgroup, emphasizing that radiation-associated gliomas represent a distinct molecular entity rather than recurrent primary tumors (5, 7). These molecular findings support the importance of comprehensive genomic profiling for accurate diagnosis, prognostication, and identification of potential therapeutic targets (5–7).

Clinically, RIGs present with seizures, focal deficits, or raised intracranial pressure. Radiologically, they manifest as heterogeneously enhancing masses with vasogenic edema, consistent with our patient's presentation (3, 9).

Management of these tumors remains challenging. Surgical resection is preferred when feasible; however, multifocal disease often limits the extent of surgery. Re-irradiation is frequently restricted due to prior craniospinal radiation exposure, while chemotherapy or targeted therapies may be considered in selected cases (1, 8, 10). Emerging molecular insights point to investigational targets such as receptor tyrosine kinase and MEK inhibition, though these remain experimental and have yet to influence standard-of-care (7).

Reported outcomes of RIGs are poor, with median survival typically ranging from 6 to 12 months; however, our patient demonstrated an even more aggressive course, succumbing within one month of diagnosis (4, 5). Recent molecular cohort studies report a median survival of approximately 6–9 months, reinforcing the aggressive nature of these tumors and aligning with the poor prognosis observed in our case (7).

Most contemporary evidence regarding RIG originates from high-income countries (HICs), where multidisciplinary survivorship programs, routine long-term neuroimaging surveillance, and widespread availability of molecular diagnostics have enabled comprehensive characterization of these tumors. Large multicenter genomic studies from North America and Europe have established the characteristic molecular profile of RIGs and reported median overall survival of approximately 6–12 months despite aggressive multimodal therapy (6, 7). Earlier recognition through structured follow-up may facilitate maximal safe resection and enrolment into clinical trials, although overall prognosis remains poor.

In contrast, published experience from low- and middle-income countries (LMICs) remains limited and mainly consists of isolated case reports and small retrospective series (12). Challenges such as limited survivorship clinics, inconsistent long-term follow-up, restricted access to MRI surveillance, molecular pathology, methylation profiling, and targeted therapies contribute to delayed diagnosis and incomplete

molecular characterization. As a result, the actual incidence of RIG in LMICs is probably underestimated, and reported survival rates tend to be poorer because patients often present with advanced or multifocal disease and have fewer treatment options (3, 12). Our case exemplifies these challenges, as comprehensive molecular profiling was not available, preventing definitive WHO molecular classification. This report thus provides valuable data from a resource-limited setting and highlights the need to improve survivorship care, enhance access to molecular diagnostics, and develop standardized surveillance strategies for pediatric brain tumor survivors in LMICs.

Conclusion

A key limitation of this report is the absence of detailed molecular testing, which restricted precise tumor classification under current WHO guidelines, and the inability to genetically compare the tumor with the original medulloblastoma to confirm their relationship. This case highlights the need for lifelong surveillance in medulloblastoma survivors, particularly in LMICs where diagnostic and therapeutic resources remain limited. Early recognition of secondary gliomas, though prognosis is poor, is critical for timely intervention and counseling.

Abbreviations

RIG	
Radiation-induced glioma	
CNS	
Central nervous system	
CSI	
Craniospinal irradiation	
HGG	
High-grade glioma	
IHC	
Immunohistochemistry	
WHO	
World Health Organization	
MMR	
Mismatch repair.	

Declarations

Ethics approval and consent to participate

The case report was conducted in accordance with the ethical standards of the institution.

Consent for publication

We obtained informed consent from the parents for publication of the patient's clinical details and relevant clinical and radiological images.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and confidentiality considerations. Still, they are available from the corresponding author on reasonable request and with appropriate institutional approval.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

U.M. collected the clinical data, performed the literature review, and drafted the manuscript. F.B. contributed to patient management and critically revised the manuscript. K.M. interpreted the neuropathology findings and revised the manuscript. B.Q. interpreted the radiation treatment details and revised the manuscript. S.A. interpreted the radiological and neuroradiological findings and revised the manuscript. S.S. contributed to neurosurgical management and critically revised the manuscript. S.U. contributed to clinical management and manuscript revision. N.M. conceived and supervised the study, critically revised the manuscript, and approved the final version. All authors reviewed and approved the final manuscript.

Acknowledgements

The authors would like to acknowledge the Departments of Pediatric Oncology, Pathology, Radiation Oncology, Radiology, and Neurosurgery at Aga Khan University Hospital for their contributions to the patient's diagnosis and management.

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Figures

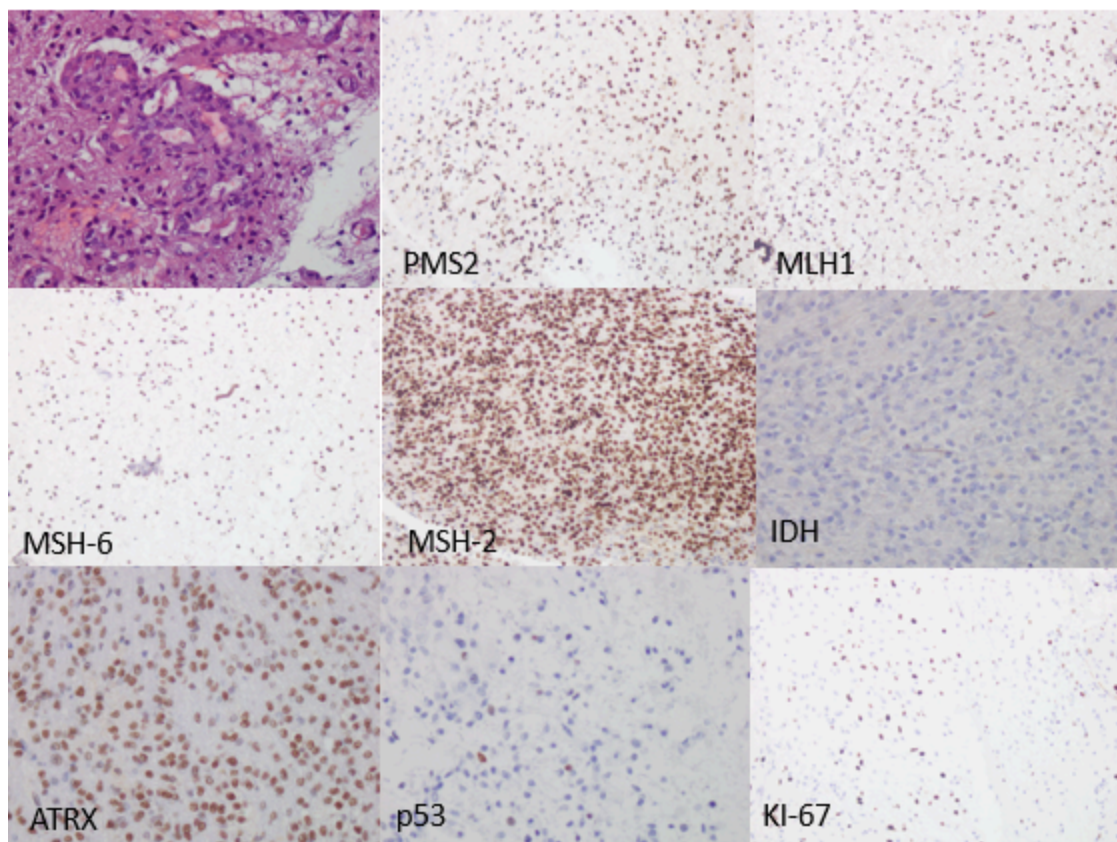


Figure 1

Immunohistochemical staining showing (a) PMS2, (b) MLH1, (c)MSH6, (d) MSH2, (e) IDH1, (f) ATRX, (g) p53, and (h) Ki-67 proliferation index.

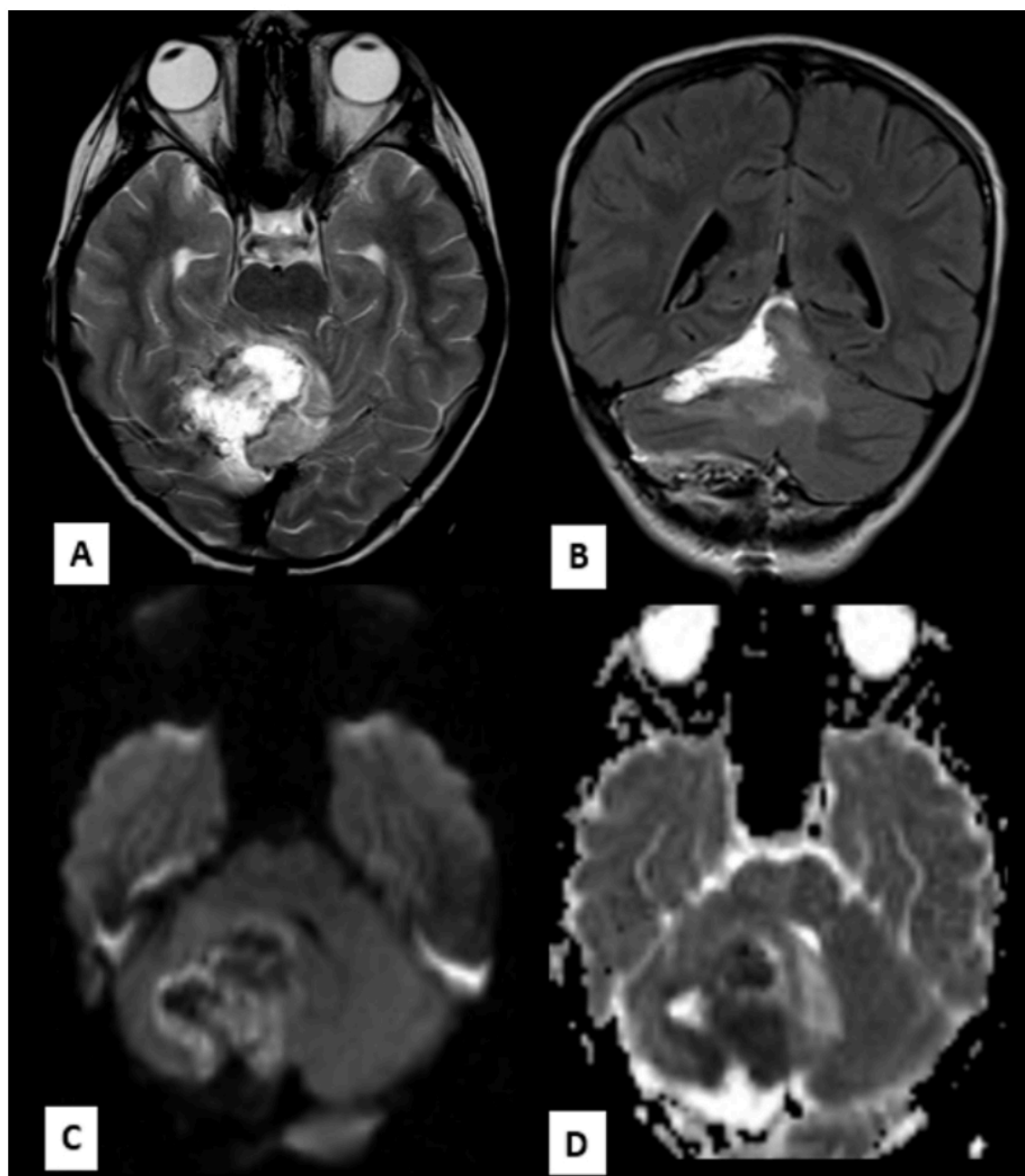


Figure 2

(A) Axial T2-weighted, (B) coronal FLAIR, (C) DWI, and (D) ADC images from the first postoperative MRI of an 9-year-old boy show a resection cavity in the right cerebellum with peripheral nodular FLAIR hyperintensity along the posterior and medial margins of the cavity, suggestive of residual disease. The lesion appears isointense on T2/FLAIR and demonstrates diffusion restriction.

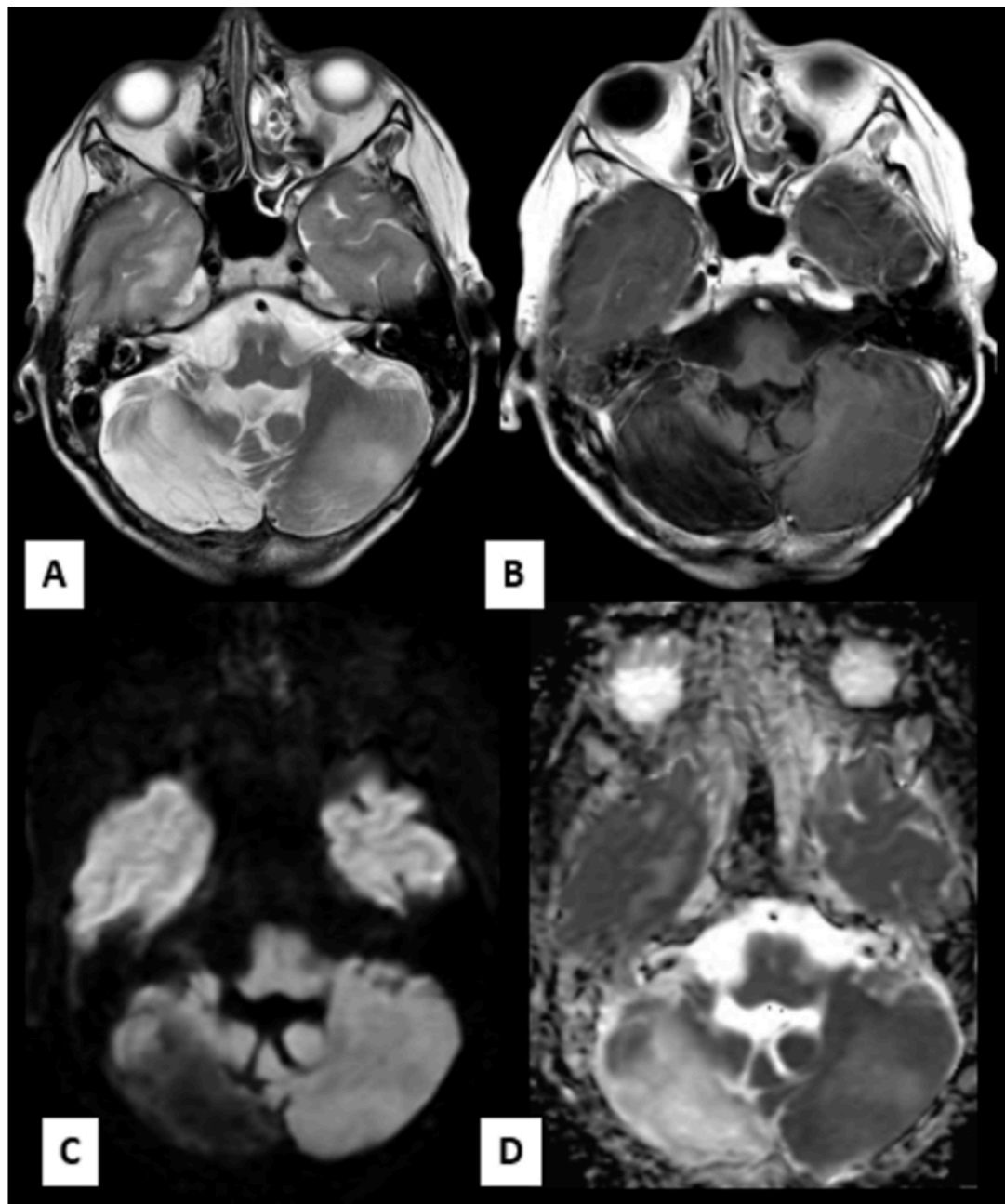


Figure 3

Figure 3a: (A) Axial T2-weighted, (B) axial post-contrast, (C) DWI, and (D) ADC images from follow-up surveillance MRI at age 19 years show encephalomalacia and gliosis at the primary tumor site, with no post-contrast enhancement or diffusion restriction, suggestive of post-treatment changes.

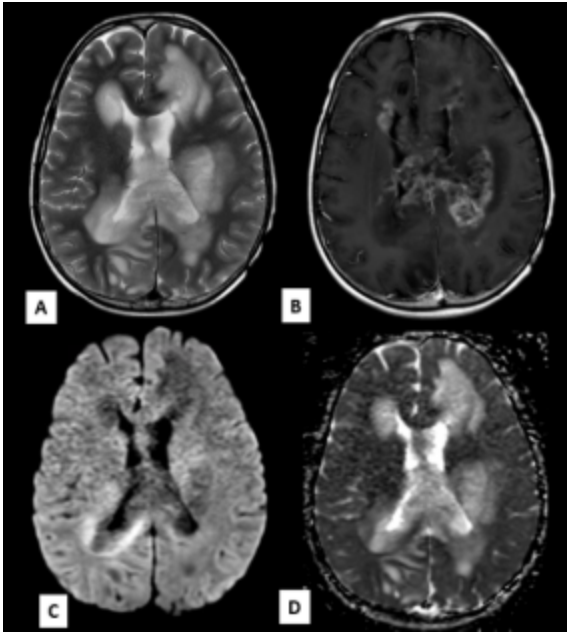


Figure 4

Figure 3b: (A) Axial T2-weighted, (B) axial post-contrast, (C) DWI, and (D) ADC images from follow-up surveillance MRI at age 19 years show a newly developed extensive lesion in the supratentorial compartment involving the corpus callosum, with pericallosal infiltration extending into the bilateral frontal and parietal lobes. The lesion demonstrates heterogeneous post-contrast enhancement and no diffusion restriction.