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Radiation-Induced Supratentorial High-Grade Glioma Following Medulloblastoma in the Right Cerebellar Hemisphere: A Case Report

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Abstract

Medulloblastoma is the most common malignant embryonal tumor of the central nervous system in the pediatric population, although it may also occur in adults. Its management requires a multimodal approach including surgical resection, craniospinal radiotherapy, and chemotherapy, which have significantly improved overall survival. However, these treatments are associated with late complications, among which radiation-induced secondary neoplasms are particularly relevant. We present the case of a 60-year-old male with a history of infratentorial medulloblastoma treated in 2020 with surgical resection, radiotherapy, and chemotherapy, who remained under active surveillance. Four years later, contrast-enhanced magnetic resonance imaging with spectroscopy revealed a new supratentorial lesion involving the genu of the corpus callosum, suggestive of a high-grade glioma. The patient underwent a right pre- and post-coronal craniotomy, where a poorly defined, grayish, avascular lesion was identified and biopsied. Histopathological and immunohistochemical analyses confirmed a high-grade glioma of glial origin, distinct from the initial medulloblastoma, supporting the diagnosis of a radiation-induced secondary neoplasm. Although meningiomas are the most frequently reported secondary tumors following craniospinal irradiation, high-grade gliomas represent a rare but aggressive complication with significant prognostic implications. This case underscores the importance of long-term imaging follow-up in patients treated with radiotherapy and highlights the need for further research to better understand the mechanisms underlying radiation-induced tumorigenesis.

Keywords

Medulloblastoma, Radiation-Induced Neoplasms, High-Grade Glioma, Post-Radiotherapy Complications, Secondary Malignancy, Neuro-Oncology

1. Introduction

Medulloblastoma is the most common malignant embryonal tumor of the central nervous system (CNS) in the pediatric population, accounting for approximately 20% of all childhood brain tumors, although it can also occur less frequently in adults [1]. It typically arises in the cerebellum and is characterized by its aggressive behavior and propensity for cerebrospinal fluid dissemination. Over the past decades, advances in neurosurgical techniques, craniospinal irradiation, and adjuvant chemotherapy have significantly improved survival rates, with long-term survival exceeding 70% in selected patient groups [2] [3].

Despite these therapeutic achievements, the increased survival of patients with medulloblastoma has been accompanied by a growing recognition of late treatment-related complications. Among these, radiation-induced secondary neoplasms represent one of the most serious and challenging long-term adverse effects [4]. Craniospinal radiotherapy, a cornerstone in the management of medulloblastoma, has been strongly associated with the development of secondary tumors, particularly in patients with prolonged survival and extended follow-up periods [5].

Radiation-induced brain tumors are defined by specific criteria, including their occurrence within the irradiated field, a sufficient latency period between radiation exposure and tumor development, histological distinction from the primary neoplasm, and the absence of genetic predisposition syndromes [6]. The most frequently reported secondary intracranial tumors following radiotherapy for medulloblastoma are meningiomas, followed by sarcomas and schwannomas, which generally exhibit a more indolent clinical course [7] [8].

In contrast, radiation-induced high-grade gliomas (RIGs) are rare but represent a particularly aggressive subgroup of secondary neoplasms. These tumors are associated with poor prognosis, rapid progression, and limited therapeutic options [9]. Their pathogenesis is not yet fully understood but is believed to involve radiation-induced DNA damage, genomic instability, and alterations in tumor suppressor genes such as TP53, as well as dysregulation of signaling pathways involved in cell proliferation and differentiation [10] [11].

Furthermore, the occurrence of secondary high-grade gliomas in supratentorial locations, distant from the original infratentorial medulloblastoma site, raises important questions regarding the mechanisms of tumorigenesis, including the potential role of neural stem or progenitor cells exposed to ionizing radiation during craniospinal treatment [12]. This phenomenon highlights the complexity of radiation-induced carcinogenesis and underscores the need for long-term surveillance strategies in this patient population.

In this context, we report a case of a radiation-induced supratentorial high-grade glioma developing four years after treatment for a cerebellar medulloblastoma, underscoring the diagnostic complexity, therapeutic challenges, and the need for long-term surveillance.

2. Clinical Case

A 60-year-old male presented in September 2020 with holocranial headache and progressive gait disturbance characterized by right-sided lateropulsion. Over the following weeks, his symptoms progressed to include ataxia. A cranial computed tomography (CT) scan revealed a posterior fossa tumor, and he was referred to the Neurosurgery Service.

The patient was admitted and underwent a midline suboccipital craniectomy with subtotal resection of the lesion. Histopathological examination demonstrated a malignant small round blue cell neoplasm composed of densely packed, poorly differentiated cells with hyperchromatic nuclei, scant cytoplasm, and high mitotic activity. Immunohistochemical analysis revealed positivity for synaptophysin, focal weak positivity for glial fibrillary acidic protein (GFAP), and S100 protein, supporting neuronal and partial glial differentiation. β-catenin showed focal cytoplasmic positivity in approximately 30% of tumor cells, and the proliferative index (Ki-67) was approximately 70%. The tumor was negative for epithelial markers. These findings were consistent with a diagnosis of medulloblastoma. Molecular subgrouping was not performed.

In December 2020, the patient was referred for adjuvant treatment. Craniospinal irradiation was planned using external beam radiotherapy, delivering a total dose of 36 Gy to the entire neuraxis in conventional fractions of 1.8 Gy per session, followed by a posterior fossa boost to a cumulative dose of 54 Gy. The treated volume included the whole brain, spinal axis, and cerebrospinal fluid pathways, consistent with standard craniospinal irradiation fields. Notably, the supratentorial corpus callosum region was encompassed within the low-dose craniospinal irradiation field.

Due to scheduling delays, radiotherapy was not initiated immediately; therefore, induction chemotherapy was started that same month with etoposide, platinum, and cyclophosphamide, consisting of two cycles prior to radiotherapy and four additional cycles as consolidation.

Follow-up imaging in July 2021 showed expected postoperative changes in the right cerebellar hemisphere, including gliosis and encephalomalacia, without evidence of tumor recurrence. Subsequent surveillance MRIs in March and September 2022 demonstrated stable postoperative findings without residual or recurrent disease, aside from chronic microangiopathic changes (**Figure 1(A)** & **Figure 1(B)**).

One year later, MRI revealed postsurgical changes in the posterior fossa; however, focal thickening of the periventricular white matter and genu of the corpus callosum raised suspicion for an infiltrative process. Given its indeterminate na-

ture, the patient was managed with close imaging surveillance during early 2024. In September of the same year, subsequent contrast-enhanced MRI demonstrated stable postoperative findings in the posterior fossa without recurrence (**Figure 1(C)**) and a new intra-axial supratentorial lesion with infiltrative characteristics apparently arising from the ependymal lining of the frontal horns of the lateral ventricles (**Figure 1(D)**).

The lesion measured approximately 3.03 × 2.77 × 1.77 cm, extending anteriorly to the cingulate gyrus and ventrally into the subcortical white matter of the right frontal lobe, with partial involvement of the frontal horns. Magnetic resonance spectroscopy demonstrated an elevated choline peak with decreased creatine, along with the presence of a lactate peak, suggestive of increased cellular proliferation and necrosis, favoring tumor progression over radiation-induced necrosis (**Figure 2(A)** & **Figure 2(B)**). No evidence of recurrence was identified at the original posterior fossa site.

Given these findings, the patient underwent a right pre- and post-coronal craniotomy in September 2024. Under general anesthesia and microsurgical technique, a transcallosal/interhemispheric approach was performed. A grayish-white, avascular lesion with irregular and poorly defined borders was identified in the corpus callosum region. A stereotactic-assisted microsurgical biopsy with limited debulking was performed due to the infiltrative nature of the lesion, obtaining tissue samples for definitive diagnosis. The procedure was completed without complications, and the postoperative course was uneventful.

Histopathological analysis of the second lesion revealed a highly cellular infiltrative glial neoplasm composed of poorly differentiated pleomorphic cells with marked nuclear atypia and high proliferative activity. Low-power examination demonstrated a densely cellular tumor with extensive necrosis (**Figure 3(A)**), while intermediate magnification showed prominent microvascular proliferation, a hallmark feature of high-grade diffuse glioma (**Figure 3(B)**). High-power views disclosed markedly atypical pleomorphic tumor cells with hyperchromatic nuclei (**Figure 3(C)**), along with increased cellular density and brisk mitotic activity (**Figure 3(D)**).

Immunohistochemical studies showed diffuse and strong positivity for glial fibrillary acidic protein (GFAP), supporting glial differentiation (**Figure 4(A)**). Tumor cells also expressed CD56; however, this finding was interpreted as nonspecific, as expression of this marker has been described in a subset of high-grade gliomas (**Figure 4(B)**).

Importantly, the tumor was negative for epithelial markers, including pancytokeratin and carcinoembryonic antigen (CEA), as well as CD45, excluding metastatic carcinoma and hematolymphoid neoplasms. Synaptophysin was negative, and CD99 showed weak focal positivity of uncertain significance. In this context, the overall histopathological and immunophenotypic profile was consistent with a high-grade glioma (WHO grade 4).

The patient was subsequently referred to the Neuro-Oncology service for comprehensive management. He was evaluated for adjuvant therapy, and at the time

of writing, remains under active oncologic treatment, with close multidisciplinary follow-up and continued imaging surveillance.

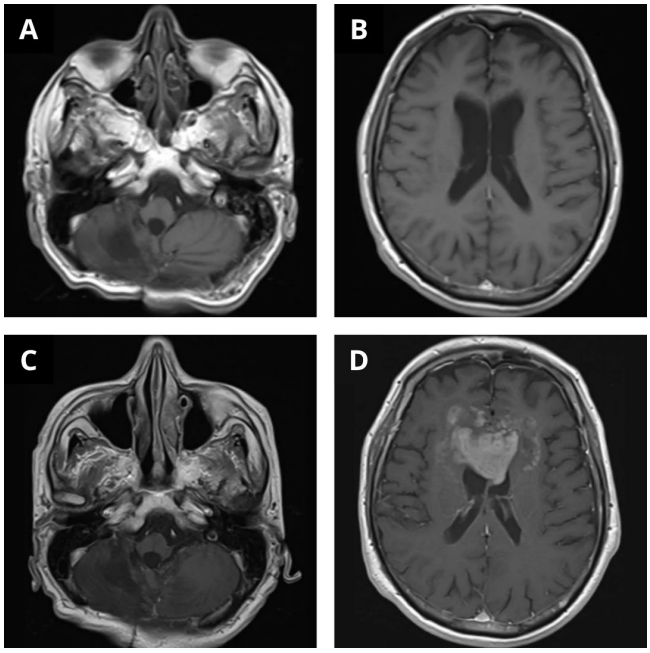

Figure 1. Axial contrast-enhanced T1-weighted brain MRI (T1 + C). (A) Infratentorial image showing postsurgical changes from the 2022 suboccipital craniectomy and tumor excision in the right cerebellar hemisphere, with cerebellomalacia, gliosis, and volume loss, without abnormal enhancement. (B) Supratentorial image from the 2022 postoperative MRI, showing no lesions or abnormal contrast enhancement at the corpus callosum. (C) Infratentorial image at 2024 follow-up showing stable postoperative changes, without evidence of recurrent enhancing lesion in the posterior fossa. (D) Supratentorial image at 2024 follow-up showing a new infiltrative, heterogeneously enhancing lesion involving the genu and body of the corpus callosum, crossing the midline ("butterfly" pattern), suggestive of a high-grade glioma.

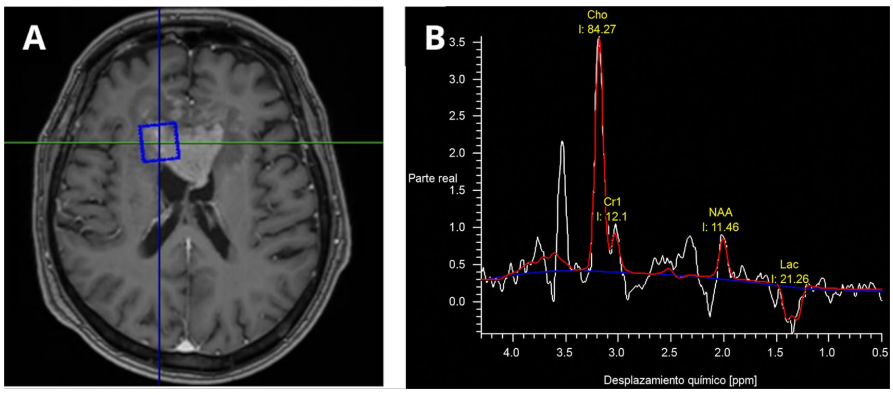

Figure 2. Magnetic resonance spectroscopy of the supratentorial lesion. (A) Axial contrast-enhanced T1-weighted MRI showing the supratentorial lesion in the genu and body of the corpus callosum, with voxel placement for spectroscopy. (B) Proton MR spectroscopy showing elevated choline (Cho), decreased N-acetylaspartate (NAA) and creatine (Cr), and a lactate (Lac) peak, consistent with increased cellular proliferation and necrosis, supporting a high-grade glioma.

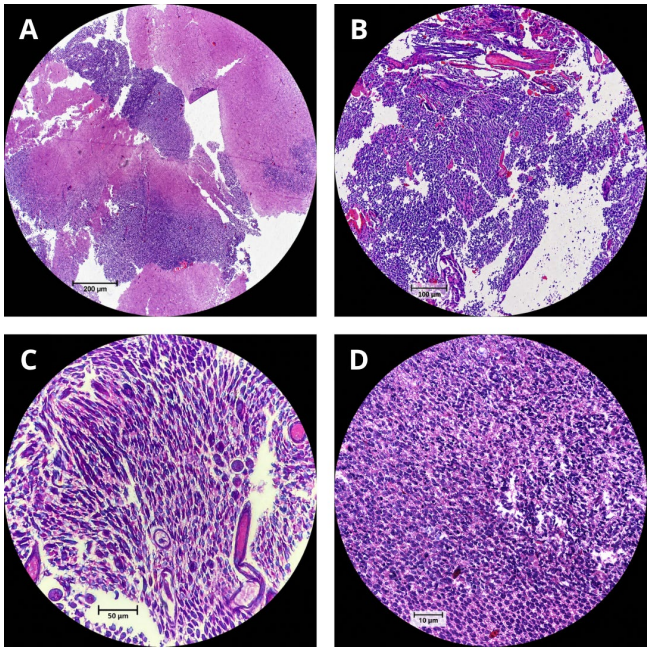

Figure 3. Histopathological findings of the supratentorial high-grade glioma. (A) Low-power H&E photomicrograph showing a hypercellular infiltrative neoplasm with extensive necrosis. (B) Intermediate magnification demonstrating marked cellularity and microvascular proliferation. (C) High-power view revealing pleomorphic tumor cells with hyperchromatic nuclei and prominent atypia. (D) Higher magnification highlighting increased cellular density and brisk mitotic activity, consistent with a high-grade glioma.

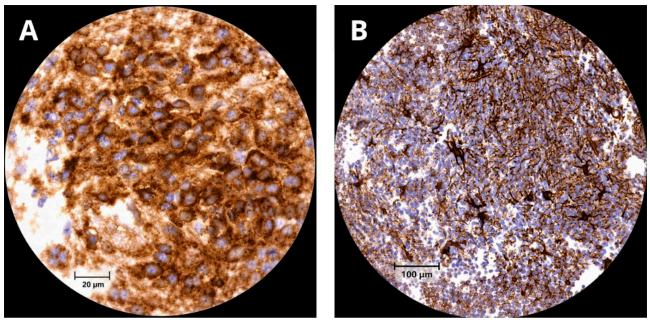

Figure 4. Immunohistochemical analysis of the supratentorial lesion. (A) CD56 immunostaining showing diffuse membranous positivity in tumor cells. (B) Glial fibrillary acidic protein (GFAP) immunostaining showing strong and diffuse cytoplasmic positivity, supporting glial differentiation.

3. Discussion

The literature describes the occurrence of gliomas following radiation therapy for medulloblastoma, supporting the concept of radiation-induced secondary neoplasms as a recognized late complication [13] [14]. Although these tumors are uncommon, their incidence appears to increase with prolonged survival, particularly in patients treated with craniospinal irradiation during earlier stages of life [14].

In the present case, radiological and immunohistochemical findings support

that the primary medulloblastoma and the subsequent high-grade glioma represent distinct pathological entities. Recurrence of medulloblastoma was considered unlikely due to the prolonged disease-free interval of approximately four years, the absence of leptomeningeal dissemination on serial neuroimaging, and the supratentorial callosal localization, which is atypical for medulloblastoma relapse. Furthermore, the infiltrative radiological pattern and glial immunophenotype of the second lesion differed significantly from the initial embryonal tumor. Treatment-related changes, including radiation necrosis or pseudoprogression, were also excluded based on the progressive growth pattern, mass effect, and metabolic profile observed on magnetic resonance spectroscopy.

This distinction is consistent with established diagnostic criteria for radiation-induced tumors, including differences in histological subtype and anatomical location [15]. In addition, clinical and family history, along with available diagnostic workup, did not reveal features suggestive of a tumor-predisposition syndrome, such as Li-Fraumeni syndrome, Gorlin syndrome, or mismatch repair–associated conditions.

However, emerging evidence from molecular studies indicates that radiation exposure may induce genomic instability and promote oncogenic transformation in susceptible neural progenitor cells, potentially linking both neoplasms through shared pathogenic mechanisms [16].

Compared with previously reported cases of radiation-induced glioma following medulloblastoma treatment, which predominantly occur in pediatric populations and frequently arise within high-dose irradiation regions, the present case is notable for its occurrence in an adult patient and for the development of a supratentorial, callosal lesion within a lower-dose craniospinal irradiation field. Additionally, the relatively short latency period of approximately four years further distinguishes this case from the longer intervals more commonly described in the literature. These features highlight the heterogeneity of radiation-induced gliomas and underscore the need for continued vigilance even in adult patients.

Furthermore, recent classifications of central nervous system tumors emphasize the importance of integrating molecular features into diagnosis, highlighting that tumors with different histological appearances may still share underlying biological pathways [17]. This raises the possibility that, despite their apparent independence, secondary gliomas may arise as a consequence of radiation-driven alterations in the tumor microenvironment and cellular differentiation processes.

Recent advances in neuro-oncology emphasize the integration of histological and molecular features for a more precise definition of glioma subtypes, as established in the 2021 World Health Organization classification of central nervous system tumors. This paradigm shift has significant clinical implications, as molecular markers such as IDH mutation status, ATRX loss, and TP53 alterations are now essential for diagnosis, prognostication, and therapeutic decision-making [18] [19]. Contemporary reviews further highlight that gliomas with distinct histological appearances may share convergent molecular pathways, underscoring

the biological complexity of these neoplasms and the role of treatment-related factors, including radiation exposure, in shaping tumor evolution [19] [20]. In this context, the absence of molecular profiling in the present case represents a limitation, as a more refined classification according to current standards could not be achieved.

Given the aggressive behavior and poor prognosis associated with radiation-induced high-grade gliomas, early identification remains critical. Therefore, long-term imaging surveillance in patients treated with craniospinal radiotherapy is essential for timely diagnosis and intervention. Additional studies are required to further elucidate the molecular mechanisms and clinical behavior of these tumors, ultimately improving risk stratification and management strategies.

4. Conclusion

Radiotherapy remains a cornerstone in the management of medulloblastoma but carries a recognized long-term risk of secondary neoplasms. This case illustrates the development of a supratentorial high-grade glioma in an adult patient following craniospinal irradiation, emphasizing the need to consider radiation-induced tumors even outside typical pediatric populations and high-dose fields. The clear histopathological distinction, atypical location, and latency period support the diagnosis of a secondary malignancy. These findings underscore the importance of prolonged, structured imaging surveillance and a high index of suspicion to enable early detection and timely intervention. Additionally, they highlight the growing relevance of integrating molecular characterization into clinical practice to better understand tumor pathogenesis and improve risk stratification in this setting.

Ethical Considerations

The authors declare that all procedures performed in this study were conducted in accordance with institutional and international ethical standards for research involving human subjects. Written informed consent for publication of clinical data and imaging was obtained from the patient. All identifying information has been removed to ensure patient anonymity. According to institutional policy, formal ethics committee approval was not required for the publication of this single-patient case report.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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