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A PMS2-Deficient Pediatric High-Grade Glioma with PI3K-Pathway Mutations and Adjacent Developmental Venous Anomaly Suggestive of CMMRD

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Case Report

Keywords: High-grade Glioma, Mismatch Repair Deficiency, PMS2 Protein, Pediatric Neuro-Oncology, Genetic Hypermutability, PI3K Pathway, TP53 Mutations, Brain Neoplasms

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A PMS2-Deficient Pediatric High-Grade Glioma with PI3K-Pathway Mutations and Adjacent Developmental Venous Anomaly Suggestive of CMMRD

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Data Availability Statement

The data supporting the findings of this report are derived from routine clinical diagnostics and contain protected health information. Therefore, they are not publicly available. De-identified data may be provided by the corresponding author upon reasonable request and subject to institutional and ethical regulations.

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Conflict of Interest Declaration

The authors declare no conflicts of interest.

Ethical Approval

This study was conducted in accordance with institutional and international ethical standards. Formal ethics committee approval was not required for this single-case report, as per our institutional policies, because all diagnostic and clinical procedures were performed as part of routine medical care and no identifiable personal information is disclosed. Written informed consent for publication of clinical details and accompanying data was obtained from the patient's parents.

Author Contributions

Ahmet ERBAĞCI: Conception of the report, acquisition of clinical and pathological data, data interpretation, drafting of the manuscript.

Tuçe SÖYLEMEZ AKKURT**:** Histopathological evaluation, immunohistochemical interpretation, molecular analysis, variant interpretation, contribution to genetic and bioinformatic data review critical revision of the manuscript.

Başak ATALAY: Radiological assessment, integration of imaging findings with clinical data, manuscript review.

Mehmet Sabri GÜRBÜZ, Fatma Betül ÇAKIR and Muhammed Emin AKSU: Integration of clinical data, manuscript review.

Gülnihal AY: Supervision, critical revision for important intellectual content, and final approval of the manuscript.

All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Keywords: High-grade Glioma, Mismatch Repair Deficiency, PMS2 Protein, Pediatric Neuro-Oncology, Genetic Hypermutability, PI3K Pathway, TP53 Mutations, Brain Neoplasms

Short Running Title: PMS2-Deficient Pediatric High-Grade Glioma

Key Points

- This case represents a pediatric high-grade glioma arising in the setting of PMS2-related constitutional mismatch repair deficiency (CMMRD).
- The tumor exhibited an ultra-hypermutated profile with co-occurring TP53, PIK3CA, PIK3R1, and PTEN mutations.
- Loss of PMS2 expression in both tumor and non-neoplastic cells was critical in establishing the diagnosis of CMMRD.
- The presence of a developmental venous anomaly may relate to underlying PIK3R1 pathway alterations.
- Routine mismatch repair immunohistochemistry is essential in pediatric high-grade gliomas, even in the absence of a family history.

Abstract

Purpose

Constitutional mismatch repair deficiency (CMMRD) is a rare hereditary cancer predisposition syndrome that frequently manifests with pediatric high-grade gliomas. However, recognition remains challenging, particularly in the absence of a clear family history. We report a pediatric high-grade glioma with PMS2 deficiency and complex molecular alterations to highlight key diagnostic clues and the importance of routine mismatch repair assessment.

Methods

Clinical, radiological, histopathological, immunohistochemical, and molecular findings of an 8-year-old girl presenting with a high-grade glioma were retrospectively evaluated. Immunohistochemistry included glial and mismatch repair markers. Targeted next-generation sequencing was performed to assess tumor mutational burden and pathogenic variants.

Results

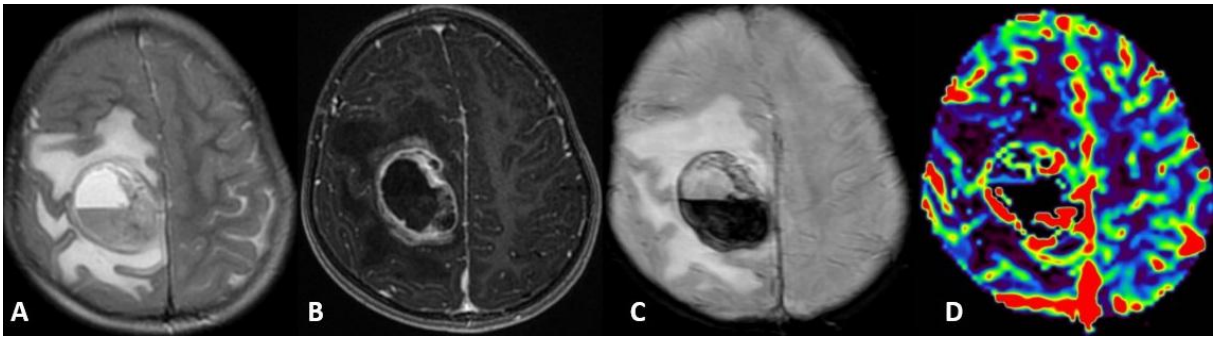
Neuroimaging revealed a right frontoparietal mass associated with an adjacent developmental venous anomaly. Histopathology demonstrated a diffuse pediatric-type high-grade glioma with pseudopapillary architecture and marked mitotic activity. Immunohistochemistry showed diffuse p53 overexpression and complete loss of PMS2 expression in both tumor and non-neoplastic cells, supporting constitutional mismatch repair deficiency. Molecular analysis revealed an ultra-hypermutated profile with a tumor mutational burden of 117.4 mutations/Mb, a pathogenic PMS2 frameshift variant, and co-occurring alterations in TP53, PIK3CA, PIK3R1, and PTEN. The presence of PI3K-pathway mutations alongside a venous anomaly suggested a potential biological association.

Conclusion

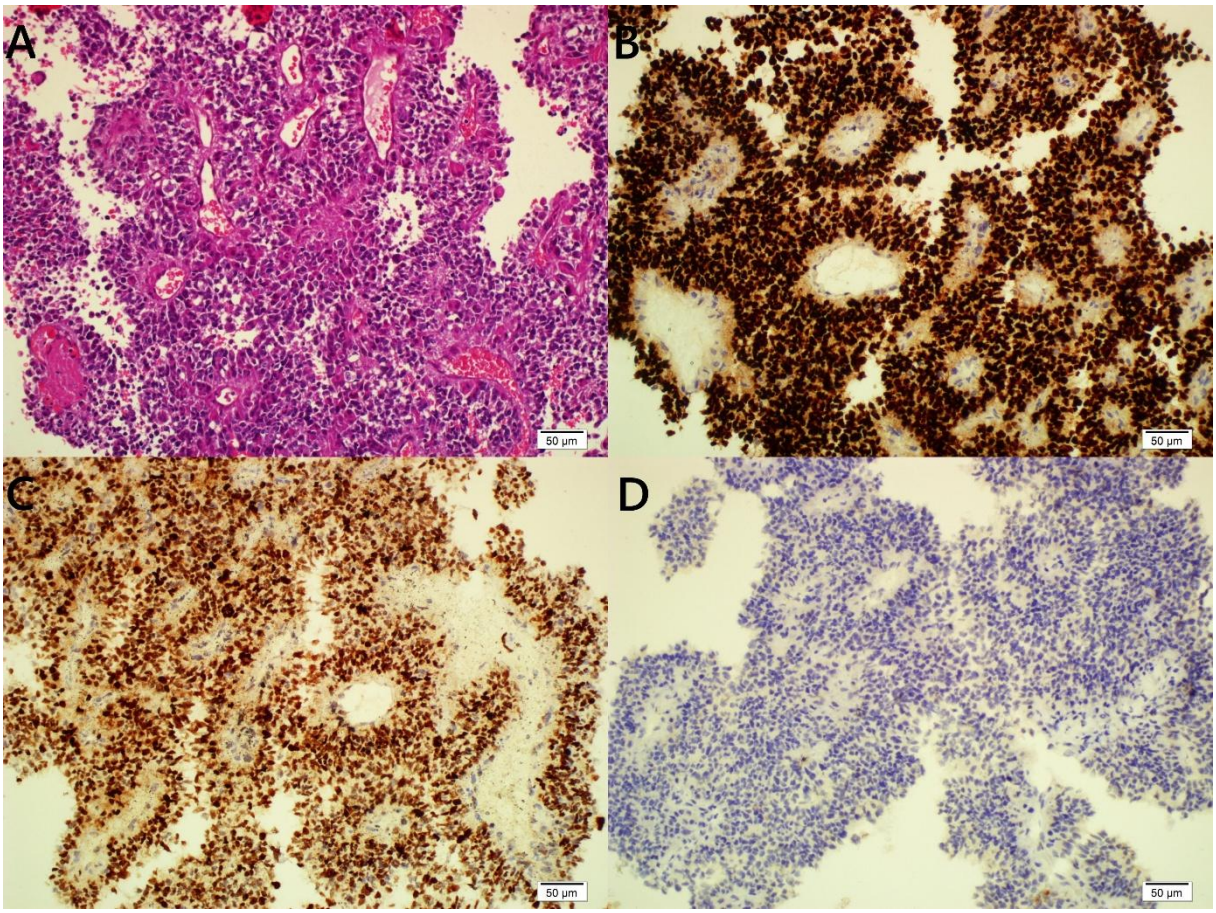
This case illustrates the characteristic clinicopathological and molecular features of CMMRD-associated pediatric high-grade glioma and underscores the critical role of routine mismatch repair immunohistochemistry. Integrated histological and genomic evaluation is essential for accurate diagnosis, appropriate genetic counseling, and potential therapeutic implications.

Case Report

An 8-year-old girl with a history of T-cell lymphoma presented with headache, inability to walk, and limb weakness, and neuroimaging revealed a right frontoparietal mass (Figure 1)



associated with an adjacent developmental venous anomaly. Her physical examination revealed café-au-lait spots resembling those seen in neurofibromatosis type 1, which are considered a clinical feature of CMMRD. Gross total resection was performed. Histopathology showed a diffuse high-grade glial neoplasm composed of atypical cells with eccentrically localized nuclei, abundant eosinophilic cytoplasm, pseudopapillary architecture, and scattered multinucleated giant cells. Mitoses numbered 7 per 10 high-power fields, and no necrosis or microvascular proliferation was observed. Immunohistochemistry demonstrated glial differentiation (GFAP+, Olig2+) and diffuse p53 overexpression (Figure 2)



. Embryonal tumors considered in the differential diagnosis were excluded by the absence of synaptophysin expression as well as retained INI1 and BRG1 immunoreactivity. IDH1-R132H staining was negative, ATRX expression was retained, and the Ki-67 proliferation index was 30%. Based on the current morphologic and immunohistochemical findings, the lesion was interpreted as a high-grade glioma. Next-generation sequencing revealed no mutations in IDH1, IDH2, or H3 genes, and the case was therefore classified as a diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype.

Given the patient's young age, prior lymphoma, tumor histology, and subtle syndromic clues—including parental consanguinity—mismatch repair (MMR) status was evaluated. Immunohistochemistry for MLH1, PMS2, MSH2 and MSH6 revealed complete loss of PMS2 expression in both tumor cells and non-neoplastic nuclei, a hallmark feature supporting constitutional rather than somatic MMR deficiency [1,2]. This pattern has been repeatedly emphasized in recent pediatric series, where PMS2 is the most frequently altered germline MMR gene and often escapes detection by standard gene panels, leading to underdiagnosis of CMMRD [2,3].

Next-generation sequencing confirmed an ultra-hypermutated tumor biology with a tumor mutational burden (TMB) of 117.4 mut/Mb, consistent with the high mutation burdens described in CMMRD-associated gliomas [4,5]. A pathogenic PMS2 frameshift variant (allele frequency 54.9%) was detected, strongly supporting a germline origin. Additional highly recurrent alterations seen in pediatric CMMRD-gliomas were present, including two TP53 mutations and multiple PI3K-pathway variants: missense and frameshift mutations in PIK3R1, a missense mutation in PIK3CA, and a frameshift mutation in PTEN. Collectively, these findings align with the molecular pattern recently characterized in hypermutated pediatric gliomas, in which TP53 inactivation and PI3K-pathway dysregulation represent early cooperating oncogenic events [4,6,7].

The identification of PIK3R1 mutations is of particular interest in this patient, as PIK3R1 has been implicated not only in PI3K-AKT signaling activation but also in the development of mixed vascular malformations and venous anomalies [8]. This correlation is striking given the presence of an adjacent developmental venous anomaly on imaging. Although DVAs are typically incidental findings, their co-occurrence with PI3K-pathway mutations has been increasingly recognized in mosaic overgrowth and vascular anomaly syndromes. The coexistence of a PIK3R1-mutated ultra-hypermutated glioma and a venous malformation in a child with biallelic PMS2 dysfunction suggests a convergence of constitutional DNA repair failure with somatic activation of PI3K signaling, potentially contributing to both tumorigenesis and vascular development abnormalities.

CMMRD clinical hallmarks were present but subtle. The patient had a prior T-cell lymphoma, a malignancy well documented in CMMRD cohorts, and parental consanguinity, both of which increase suspicion in retrospect. Recent multicohort studies show that many pediatric patients with CMMRD present initially with brain tumors, and a significant proportion have no family history, underscoring the importance of routine MMR immunohistochemistry in pediatric high-grade gliomas regardless of clinical context [1,4,6]. Early identification of MMR deficiency is clinically meaningful: it triggers germline testing, informs cancer surveillance for relatives, and carries therapeutic implications, as immune checkpoint inhibitors have shown improved outcomes in MMR-deficient gliomas across age groups [1].

This case contributes to the growing recognition that pediatric high-grade gliomas with constitutional MMR deficiency constitute a biologically distinct subgroup. They frequently exhibit ultra-hypermutation, TP53 co-mutation, PI3K-pathway alterations, and unusual vascular features, and they may occur in children previously treated for hematologic malignancies. As recommended by recent prospective pediatric high-grade glioma screening studies, MMR immunohistochemistry should be routinely incorporated into the diagnostic work-up of all pediatric high-grade gliomas, particularly in IDH-wildtype, H3-wildtype tumors and in cases with early-onset malignancies or syndromic clues [1,6]

At three months of follow-up, the patient remains under clinical surveillance. Ongoing management will require multidisciplinary coordination, including genetic counseling for the family, assessment for additional CMMRD-associated malignancies, and consideration of immunotherapy should recurrence occur.

This report underscores the necessity of heightened awareness of CMMRD in pediatric diffuse high-grade gliomas, particularly when PMS2 loss extends to non-neoplastic tissue and when PI3K-pathway mutations or vascular anomalies are present. The integration of histopathology, immunohistochemistry and genomic data remains central to the accurate recognition of this biologically and clinically consequential entity.

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Figure Legends

- Figure 1: Right frontoparietal convexity–localized tumor demonstrating high-grade Magnetic Resonance imaging characteristics.
    - 1A: Axial T2-weighted image shows hemorrhagic fluid–fluid levels with extensive surrounding edema.
    - 1B: Axial post-contrast T1-weighted image demonstrates a heterogeneously enhancing, highly vascularized mass.
    - 1C: DSC perfusion MRI (Dynamic Susceptibility Contrast Perfusion Magnetic Resonance Imaging) reveals prominent perfusion in the peripheral solid portions of the lesion.
    - 1D: SWI (Susceptibility-Weighted Imaging) depicts intratumoral hemorrhage.

- Figure 2A: Tumor cells with eccentrically located nuclei forming a pseudopapillary architecture (H&E, ×200).
- Figure 2B: Diffuse strong nuclear immunoreactivity for Olig2 in tumor cells (×200).
- Figure 2C: Diffuse p53 overexpression in tumor cells (×200).
- Figure 2D: Loss of nuclear PMS2 expression in both tumor and stromal cells (×200).