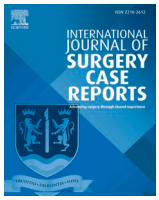
International Journal of Surgery Case Reports 122 (2024) 110148

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr



Case report

Primary mismatch repair-deficient IDH-mutant astrocytoma in child: Unusual entity

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ARTICLE INFO

Keywords:
Mismatch repair-deficient
IDH-mutant
Astrocytoma
Child

ABSTRACT

Introduction: "Primary Mismatch Repair-Deficient IDH-mutant Astrocytoma" (PMMRDIA) is a newly identified high-grade glioma with a poor prognosis. It has not been officially recognized as a distinct entity in the 5th edition of the WHO Classification of Central Nervous System Tumors 2021, making its diagnosis challenging.
Case presentation: To highlight this entity, we present the case of a 7-year-old boy with a family history of cerebral tumor among the father's relatives and first-degree parental consanguinity. He experienced increased intracranial hypertension and inguinal café-au-lait macules. Brain imaging revealed a cystic and solid mass with irregular enhancement in the left parietal lobe, indicating a possible Pilocytic astrocytoma. The final diagnosis of PMMRDIA was confirmed through histological, immunohistochemical, and molecular analysis.
Clinical discussion: This tumor is mainly observed in children and is characterized by microsatellite instability (MSI) and high tumor mutational burden (TMB). MSI is known to occur in recurrent IDH-mutant gliomas as a resistance mechanism towards alkylating chemotherapy.
Conclusion: In PMMRDIA, MSI can be a good predictive biomarker for responding to immunotherapy, which could improve the outcome of these children.

1. Introduction

Base substitution and insertion-deletion mismatches generated during DNA replication are corrected by the DNA mismatch repair (MMR) pathway. Germline mutations in one of the four MMR genes (MLH1, MSH2, MSH6, and PMS2) cause cancer predisposition [1]. This condition is associated with a different spectrum of disease; high-grade gliomas (HGGs) are the most common malignancy described [2]. Recent studies have demonstrated a potential new entity dubbed "Primary MisMatch Repair Deficient IDH-mutant Astrocytoma" (PMMRDIA), a group of IDH-mutant astrocytomas arising in the presence of germline mismatch repair (MMR) mutation deficiency [3]. These cases occurred almost exclusively in children and young adults with decreased rates of *MGMT* promoter methylation, a separate DNA methylation cluster from other IDH-mutant astrocytomas, and a poor prognosis [3]. Our paper aims to present a new case of PMMRDIA, highlighting the importance of researching MMR status in pediatric high-grade glioma, especially in the context of parental consanguinity.

2. Case presentation

We are presenting a case of PMMRDIA in a 7-year-old boy who was admitted to the Department of Neurosurgery at Rabat Specialties Hospital (HSR) in Morocco in October 2022. The patient exhibited signs of increased intracranial hypertension, such as headaches, dizziness, and impaired consciousness, but did not display any sensorimotor deficit or seizures. Upon admission to the emergency department, the patient had a Glasgow Coma Scale (GCS) score of 9. Family history reported a cerebral tumor in an 18-year-old female among the father's relatives and first-degree parental consanguinity. Clinical examination found inguinal café-au-lait macules.

The MRI showed a well-defined cystic mass in the left parietal lobe, with a solid component. It appeared slightly hypointense on T1 and hyperintense on T2 and was strongly contrast-enhanced, which may indicate a Pilocytic astrocytoma (Fig. 1). The patient underwent an emergency craniotomy, initially puncturing the cystic component and then undergoing subtotal resection of the solid part.

Our Department of Pathology of HSR received grayish and myxoid tumor fragments, which varied in size, with the largest measuring 1.0 ×

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https://doi.org/10.1016/j.ijscr.2024.110148
Received 30 June 2024; Received in revised form 1 August 2024; Accepted 8 August 2024
Available online 10 August 2024

0.3 × 0.2 cm and the smallest measuring 0.1 × 0.1 × 0.1 cm. They were examined under a microscope after being formalin-fixed and paraffin-embedded. The histological analysis revealed the presence of a high-grade glioma with higher cell density, pleomorphic nuclei, and numerous multinucleated giant cells. Additionally, microvascular proliferation and geographic necrosis were observed (Fig. 2).

In immunohistochemistry, tumor cells diffusely expressed GFAP, Olig 2, IDH1 R132H, and P53, while ATRX expression was lost. Ki-67 labeling index was high (Fig. 3). Thus, the diagnosis of High-grade IDH1-mutant Astrocytoma (grade 4) was proposed. However, this glioma occurs in a young child with parental consanguinity, which suggests a context of tumor predisposition syndrome. Therefore, by Immunohistochemistry (IHC), we analyzed the expression of the MMR proteins (MLH1, PMS2, MSH2, MSH6). Among the four anti-MMR protein antibodies, we observed a complete loss of PMS2 expression (Fig. 4A–D), confirming the MMRD phenotype. Further, Polymerase Chain Reaction (PCR) analysis indicated a microsatellite instability-high (MSI-H) phenotype. There was no lymphocytic infiltrate within the tumor, and CD3 and PDL-1 were not expressed (Fig. 4E and F).

Gene sequencing mutational burden and genetic consulting were not carried out due to a lack of technical platforms.

Based on these features, the diagnosis of "Primary Mismatch Repair-Deficient IDH-mutant Astrocytoma" arising in Constitutional Mismatch Repair-Deficient was made.

The analysis of MGMT promoter (MGMTp) methylation did not detect hypermethylation of MGMTp. As a result, chemotherapy was not given. However, the patient received 33 radiotherapy sessions (59.4 Gy) from January 2, 2023, to February 16, 2023. Although immunotherapy was recommended; it could not be administered due to lack of means. Eight months after being diagnosed, he had a relapse with tumor progression, which ultimately led to his death despite a second attempt at Gamma radiosurgery.

This case has been reported in line with the SCARE criteria [4].

3. Discussion

Pediatric high-grade gliomas (pHGGs) encompass a heterogeneous group of tumors [5]. They show frequent alterations in the histone genes causing epigenetic dysregulation, in contrast to the more known IDH mutations and epidermal growth factor receptor (EGFR) amplification in adult HGG. This molecular evidence emphasizing the distinctive nature of pediatric HGG formed the basis for the delineation of the pediatric type of HGG as a distinctive group of tumors in the current fifth edition of WHO classification of the central nervous system tumors [6].

In this case, we initially classified the glioma as high-grade IDH1-mutant Astrocytoma (grade 4). However, IDH1 mutations are rare in pediatric gliomas, accounting for only 0–17 % of cases [7], with a higher rate among adolescents [8]. The clinical implications of IDH1 mutations in the pediatric population are far less understood. IDH1 mutant pediatric gliomas will likely behave differently from other pediatric gliomas [7]. In this particular case, this high-grade IDH1-mutant Astrocytoma was associated with a MisMatch Repair Deficiency (MMRD).

The MMRD phenotype is caused by loss of DNA Mismatch Repair (MMR) function either by germline and somatic mutation in one of the four human MMR genes MSH2, MLH1, MSH6, PMS2, or by promoter methylation of MLH1 [9].

Mutations in these genes are implicated as driver oncogenesis and result in the accumulation of errors in DNA replication, especially at the microsatellite end of chromosomes which is known as microsatellite instability (MSI). MSI has been described in HGGs with a frequency ranging from a percentage close to 0 % to more than 40 %. MSI-related gliomas are more frequent in children than in adults. Variants in MMR genes may be sporadic or inherited as a monoallelic germline variant (Lynch syndrome) or biallelic variant (constitutional mismatch repair deficiency, CMMRD) [5].

In our case, the MMRD-IDH1 mutant Astrocytoma appeared in a young child with parental consanguinity and cafe-au-lait macules. Histologically, it showed numerous giant multinucleated cells, indicating a context of Constitutional mismatch repair deficiency (CMMR) [6]. These characteristics are consistent with "Primary Mismatch Repair Deficient IDH-mutant Astrocytoma" (PMMRDIA), as described in the literature. This potential new entity has been demonstrated by recent studies [3] as a group of IDH-mutant astrocytomas arising in the presence of germline mismatch repair (MMR) mutation deficiency; in the context of Lynch Syndrome or CMMRD [10]. These tumors occurred almost exclusively in children and young adults (median age 14 years old, range 9–54 years old), with a separate DNA methylation cluster from other IDH-mutant astrocytomas [10].

Histologically, this glioma does not differ from an HGG, it shows brisk mitotic activity, necrosis, and microvascular proliferation but it exhibits increased rates of atypical morphology including giant cells and primitive neuronal features [10].

In the study by Suwala AK et al. 3, PMMRDIA demonstrates the worst clinical outcome among all IDH-mutant gliomas, with a mean overall survival of only 15 months [3]. It is characterized by a high frequency of hypermutant phenotype and often a massive Tumor Mutation Burden (TMB) with microsatellite instability, a low rate of MGMT promoter methylation, and resistance to therapies [10]. Alkylating anti-neoplastic agents such as Temozolomide are less effective in MMR-deficient tumors, and might even provide a growth advantage to tumor cells. Therefore, this drug should be avoided in patients with CMMRD [1]. However, MMRD gliomas linked to high TMB and MSI phenotype may

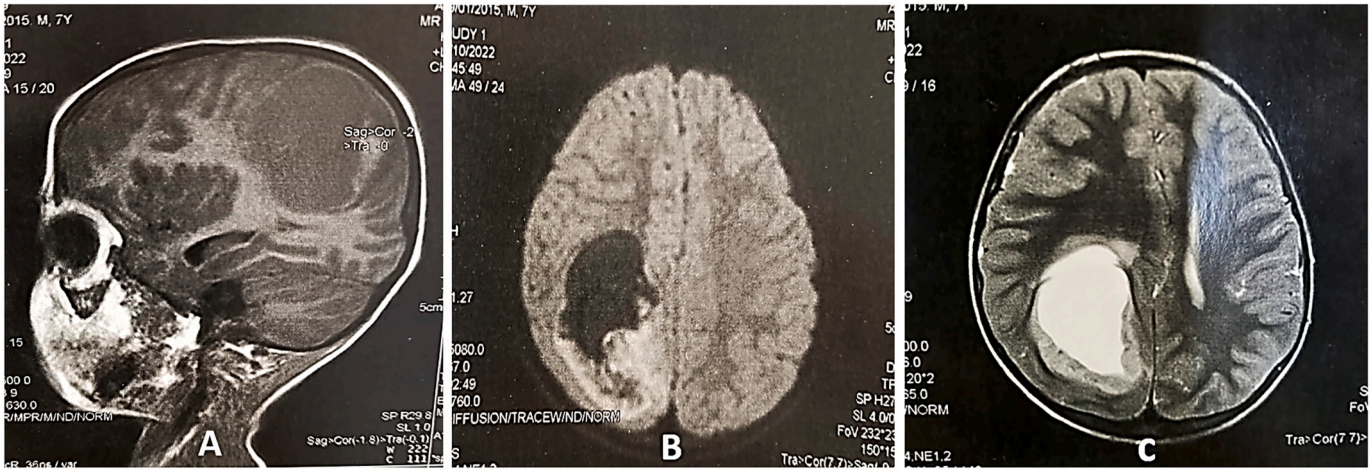

Fig. 1. MRI showing a parietal mass (A) with cystic and solid components (B), and irregular contrast enhancement (C).

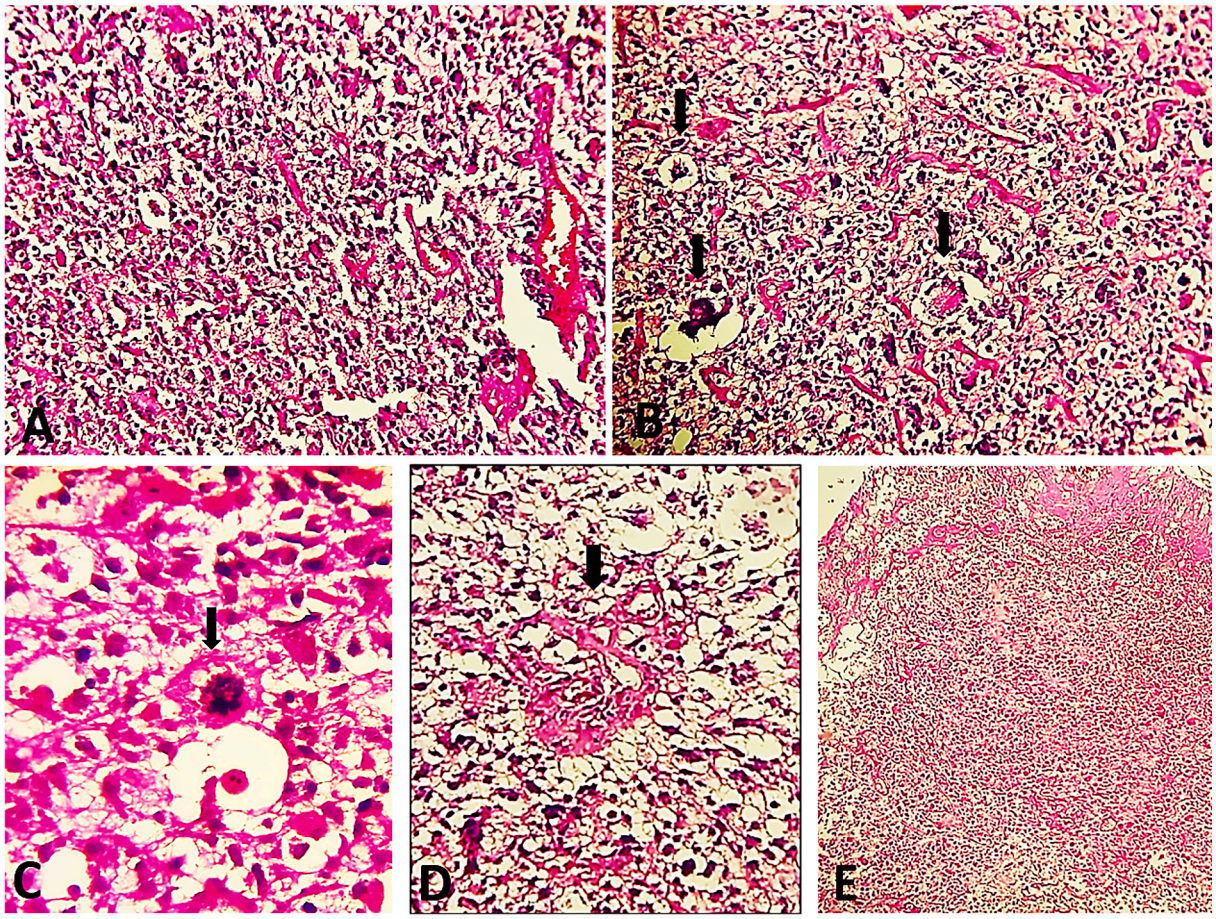

Fig. 2. (A) Histological analysis showing a high-grade glioma with increased cellularity, (B) pleomorphic nuclei and numerous multinucleated giant cells (arrow) (Hematoxylin-Eosin ×20), (C) brisk mitotic activity (arrow) (Hematoxylin-Eosin x40), (D) microvascular proliferation (arrow) and (E) geographic necrosis (arrow) (Hematoxylin-Eosin x20).

respond to immunotherapy [11]. A study by Léa Guerrini-Rousseau et al. [1] suggested that immune checkpoint inhibitors (PD1/PD-L1 inhibitors) could prolong the survival of patients.

In our case, the benefits of immunotherapy have not been evaluated because it could not be administered due to a lack of means. This case clearly illustrates the diagnostic importance of detecting MMRD status in every high-grade pediatric astrocytoma, especially in cases of parental consanguinity, by using simple and inexpensive immunohistochemical staining [12]. This will help guide early diagnosis and therapy.

4. Conclusion

The diagnosis and management.t of pediatric high-grade gliomas (HGGs) in the setting of tumor predisposition syndrome are quite challenging. Early identification of such tumors could lead to better prognoses. "PMMRDIA" is a newly recognized condition that requires further study in larger multi-institutional series to understand its biological behavior fully.

Consent

Written informed consent was obtained from the patient's legally authorized representative for publication of this case report.

Ethical approval

Ethical approval is not applicable. The case report is not containing any personal information. Our institution of Ibn Sina University Hospital does not require ethical approval for reporting individual cases or case series.

Funding

The authors didn't use any sources of funding, and this study has no sponsors.

Author contribution

All authors have read and approved the final manuscript. HE wrote the manuscript; NC revised and supervised the work.

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Conflict of interest statement

There are no conflicts of interest for authors in this study.

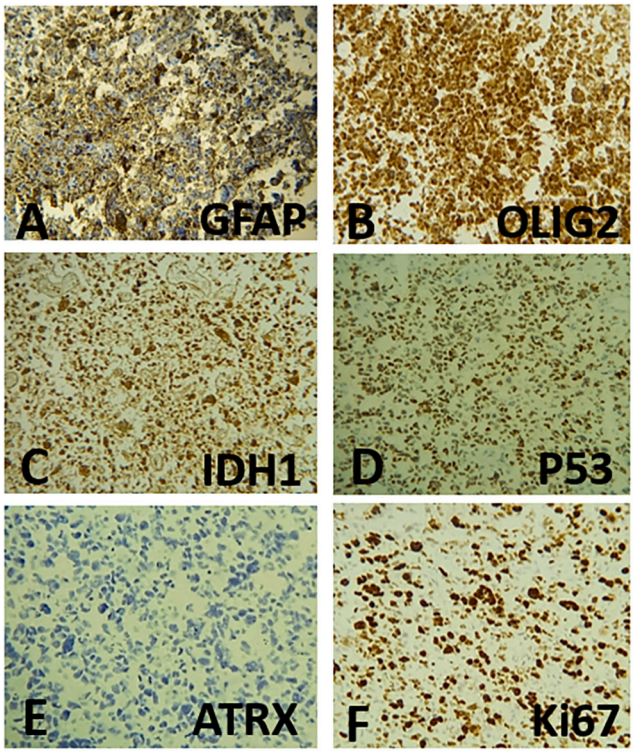

Fig. 3. At immunohistochemistry, tumor cells express GFAP (A), Olig 2 (B), IDH1 R132H (C), and P53 (D), while ATRX (E) expression is lost. Ki-67 (F) labeling index is high.

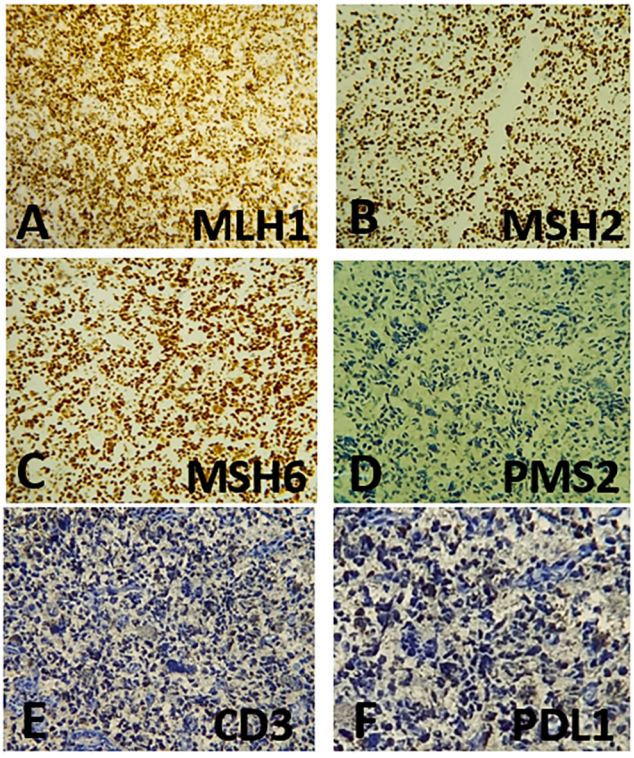

Fig. 4. Among the four anti-MMR protein antibodies: anti-MLH1 (G), anti-MSH2 (H), anti-MSH6 (I), and anti-PMS2 (J) that are retained; PMS2 is lost. CD3 (K) and PDL-1 (L) are not expressed.

Data avaibility statement

No new data were generated or analyzed in support of this research. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgement

Declared none.

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