



# Primary cervical glioblastoma multiforme as a presentation of constitutional mismatch repair deficiency: Case report and literature review

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## ABSTRACT

**Introduction and importance:** Primary Glioblastoma Multiforme (GBM) of cervical spinal cord represent an extremely rare type of tumors in the pediatric age group. Constitutional mismatch repair deficiency (CMMRD) patients are known to develop uni- or multiple synchronous-high grade gliomas in the brain.

**Case presentation:** The authors report a 23 month old child presented with bilateral upper limb weakness for 7 days with imaging evidence of intramedullary mass lesion that extends from the level of the C3 to C7. The patient underwent excisional biopsy from C3 to C7 and laminoplasty. Immunohistology confirmed primary cervical GBM.

**Clinical discussion:** Constitutional mismatch repair deficiency is cancer tending syndrome associated with broad spectrum of malignancies. Screening for CMMRD is not a daily practice in oncology and thus prevalence might be underestimated. To authors' knowledge, no prior primary cervical GBM in CMMRD syndrome.

**Conclusion:** This report highlights the challenges of CMMRD polymorphic presentations, diagnosis, complications, management and surveillance.

## 1. Introduction

Constitutional mismatch repair deficiency (CMMRD) syndrome is a state of genetic disposition for cancer formation, that is most frequent in the first two decades of life. Affected children have biallelic germline mutations of MMR genes; which are responsible for DNA repair through a process called "mismatch repair" therefore patients have poor or deficient correction of DNA-replication errors. This work has been reported in line with the SCARE 2020 criteria [1,2].

The spectrum of CMMRD syndrome is broad involving different malignancies; Central nervous system (CNS), gastro-intestinal (GI), vascular, hematologic malignancies and other types of carcinomas or sarcomas. Solitary or multiple synchronous tumors can be the presentation [3,4]. CMMRD diagnosis tends to be delayed because it does not have a characteristic sign or finding and requires extensive immunohistopathologic and genetic testing to establish the diagnosis. CMMRD syndrome has some concomitant nonspecific physical features such as café-au-lait.

Increased incidence of CMMRD is associated with history of consanguinity and societies of closed marriage [5]. The general outcome and prognosis is poor, with 5-year survival after the first brain tumor almost 22% [3].

Herein, we report and describe a case of 23-month old male patient, who is medically and surgically free, presented to the emergency department with bilateral upper limb weakness for 7 days.

## 2. Case presentation

We reported a case of a 23-month old male, medically and surgically free with no known allergies; presented to the emergency department with history of bilateral upper limb weakness for 7 days prior to admission. Weakness started initially on the right side 7 days ago and progressed over time to both upper limbs since 2 days, weakness started on the shoulder and gradually extended further below to the hands. Parents reported a stiff neck posture with abnormal tilted posture, difficulty walking, decreased activity for the last 2 days. Parents denied

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history ill-contact, history of similar presentation or malignancies in first-degree relatives. Parents reported extended history of consanguinity.

No history of trauma, no fever, no history of recent upper respiratory tract infection, no vomiting, no change on bowel habit, no blurry vision, no diplopia, no headache, no alteration of level of consciousness, no decrease in oral intake, no weight loss, no night sweats.

On physical examination, The patient was oriented, conscious and alert with no signs of dehydration or respiratory distress. Hypopigmented patch and café-au-lait spot were noticed lateralized to left hemi-abdomen and right calf respectively, but no lymphadenopathy (Fig. 1). Chest examination revealed clear vesicular breathing sounds with good air entry bilaterally, heart sounds were appreciated in timing, character, intensity and location. Abdomen was soft and lax, normal other parameters. No lymphadenopathy.

Neurological exam showed bilateral upper limb weakness more on the right side, with decreased tone and bilateral C5 decreased sensation. The patient was able to move both lower limbs symmetrically and spontaneously. Pupils were bilaterally reactive. Cranial nerves were grossly intact.

Appropriate lab investigation were ordered along with brain and spine MRI with contrast showed evidence of intramedullary mass lesion that appears hyperintense on T2 and low on T1 causing expansion of the cervical cord. That is associated with cord edema. The lesion extends from level of the C3 to C7 and shows peripheral enhancement on post-contrast images. But there is no evidence of hemorrhage. There is diffuse leptomeningeal enhancement along the length of the cord and conus medullaris, also involving the brainstem. Findings are suggestive of spinal cord astrocytoma, another differential diagnosis includes ependymoma, with drop metastasis along the neuroaxis as described (Fig. 2 (A,B,C)).

Therefore the patient was planned for excisional (decompressive) biopsy from C3 to C7 and laminoplasty with intraoperative neuro-monitoring. Surgery was performed by the neurosurgery consultants and chief resident at a tertiary teaching hospital. Postoperatively course was unremarkable with mild improvement in the motor function of both upper limbs (Fig. 2(D)).

Histopathology reports revealed a cellular glial tumor with scattered mitotic figures, vascular proliferation and necrosis. Review of the immunostains performed in the our university hospital lab revealed that the tumor cells are positive for GFAP, vimentin, negative CD31, CD 34, S100, H3K27 M, BRAF (V600E) and p53 (Fig. 3). Mismatch repair protein immunostains showed retained MLH1 and complete loss of MSH2. The proliferation index is estimated at 5% (Fig. 4).

Immunohistochemistry testing for mismatch repair proteins: MSH6 and MSH2: loss of nuclear expression in both the tumor and the normal tissue including neurons, epithelial cells and inflammatory cells consistent with the biallelic mismatch repair deficiency syndrome (Fig. 4). Diagnosis established as high grade glioma most consistent with

glioblastoma, WHO grade IV. The patient start chemotherapy 20 days after surgery in King Hussein cancer center.

### 3. Discussion

DNA replication is a tight process with highly conserved biological pathways to maintain DNA fidelity and exactness. DNA mismatch repair system (MMR) is essential pathway that corrects the incident base substitution and insertion-deletion loops. The DNA mismatch repair system constitute of the namely genes mutL homolog1 (MLH1), mutS homolog1 (MSH2), pms2 c-terminal like pseudogene (PMS2), or mutS homolog6 (MSH6) [6].

Patients with either mono-allelic or bi-allelic MMR mutations have deficient or inadequate DNA replication-errors correction which results in hypermutated genetic component with various point mutations and microsatellite instable sequences [7].

Constitutional mismatch repair deficiency (CMMRD) is a childhood cancer predisposing syndrome caused by germline biallelic autosomal recessive mutations or by compound heterozygous mutations in the MMR genes. The prevalence of this of this syndrome is argued to be underestimated. Most of the incident cases are linked to areas and families where consanguinity is widely practiced such as middle east and south Asia; 53% of CMMRD malignancy cases were associated with familial consanguinity [3,5].

Children with Germline CMMRD syndrome are predisposed to develop a board spectrum of tumors; central nervous system (high grade gliomas, meningiomas, plexiform neurofibroma), hematological (lymphoma and leukemia), genitourinary and gastro-intestinal tract tumors (adenomas, adenocarcinoma). However, multiple supratentorial tumors of high grade glioma was the most specific dysplastic feature of CMMRD [4]. In this case, the patient had a cervical high grade glioma most suggestive of glioblastoma which seems to be the first case reported with thus circumstances.

The incidence of primary high grade glioma at this pediatric age is extremely rare in population with functioning mismatch repair systems [8] and at age of 23 month, even, far more advanced onset in comparison with CMMRD records which tend to present at older age (median 9.2 years) [3].

Although CMMRD syndrome causes a childhood onset tumors, a less penetrant phenotype was described; of which, tumors go unnoticed till third or fourth decade of life [9]. Less-penetrant phenotype of CMMRD syndrome is less clear; since it would intersect with known autosomal dominant mismatch repair deficiency of lynch syndrome, adenomatous polyposis and other hereditary syndromes. Despite these similarities, CMMRD syndrome patients usually are less likely to have family history of suspicious malignancies.

In addition to the cancer tendency, CMMRD syndrome patients have cutaneous, vascular, neurological and hematologic findings; yet none of these features is a criterion for diagnosis; frequent cutaneous features of hypo- or hyperpigmentation spots, café-au-lait spots, less frequently freckles and Lisch nodules [2]. Agenesis of corpus callosum and (IgG2, IgG4, IgA) deficiency have been also reported [2,10].

Screening for CMMRD syndrome is not a routine histopathologic practice neither a molecular guideline. Malignancies in the first 2 decades of life or multiple synchronous tumors, hypermutated tumors, loss of MMR proteins on normal tissue, lynch associated tumor, hematologic malignancy in absence of radiation history, presence of cutaneous café-au-lait sign, hypo/hyper-pigmented lesions without molecular NF1, and paternal consanguinity may be strongly suggestive for clinician to consider CMMRD syndrome [2].

Immunohistochemistry modalities are used nowadays to select and inspect CMMRD which show loss of MMR proteins in both of normal and malignant tissues. Establishing a diagnosis of CMMRD requires genetic testing that confirm biallelic mutations in one gene or compound heterozygous mutations in the MMR genes [11].

Current guideline for CMMRD tumors comprise a combination of

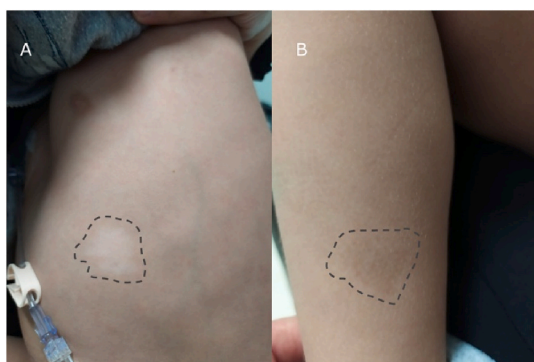


Fig. 1. Hypopigmented patch was noticed lateralized to left hemi-abdomen (A) and café-au-lait spot was noticed on right calf.

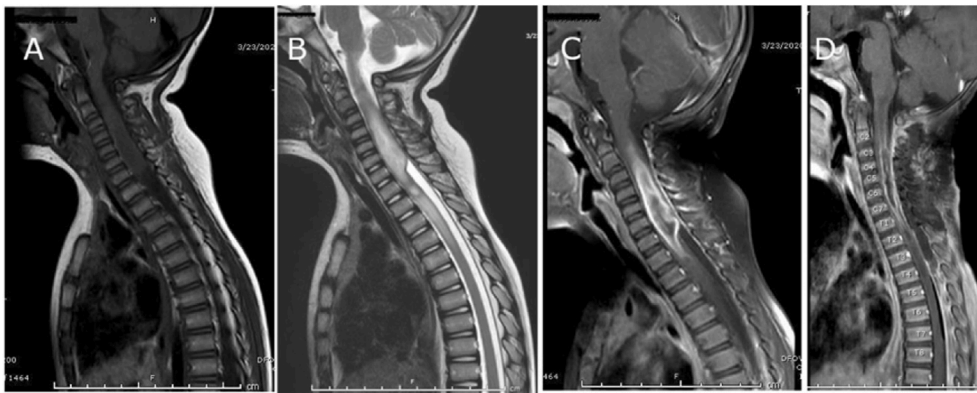


Fig. 2. Pre-operation MRI, intramedullary mass lesion that appears hyperintense on T2 (B) and low on T1(A) causing expansion of the cervical cord. The lesion shows peripheral enhancement on T1 postcontrast images (C).T1 post operative MRI study shows changes and evidence of intra-axial cervical tumor debulking. (D).

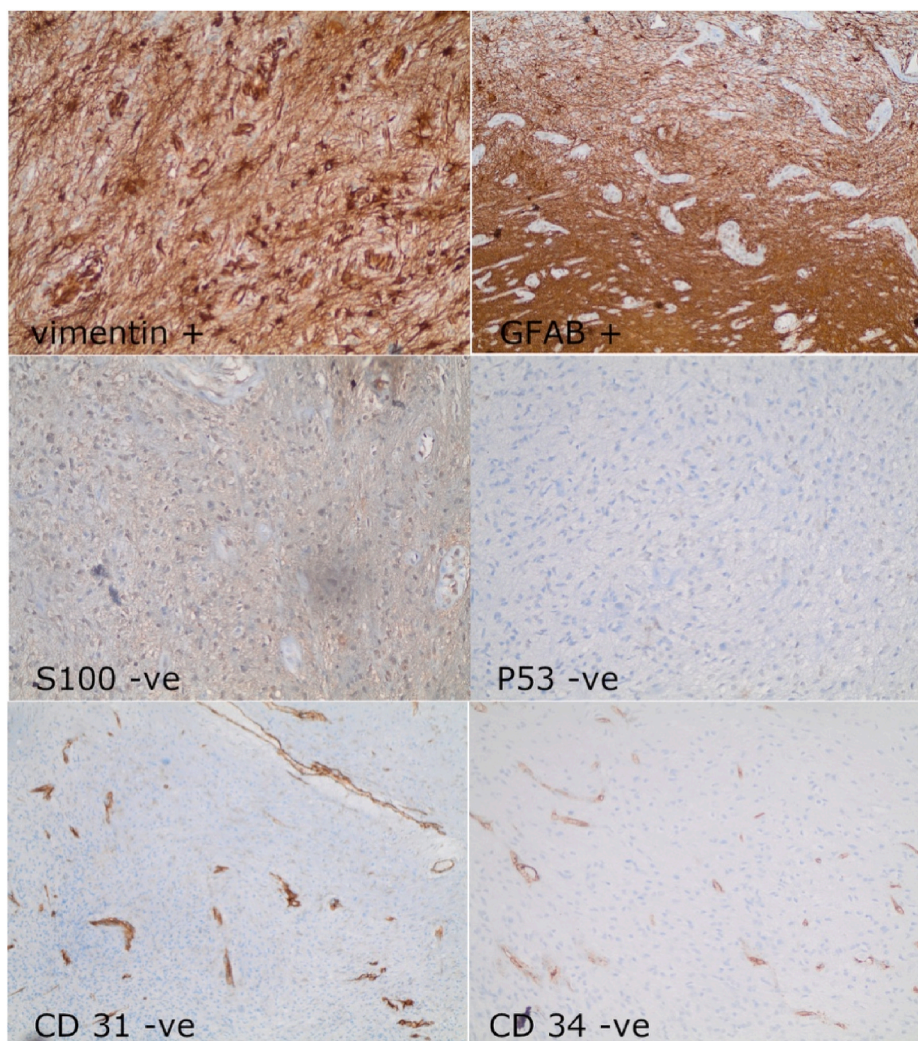


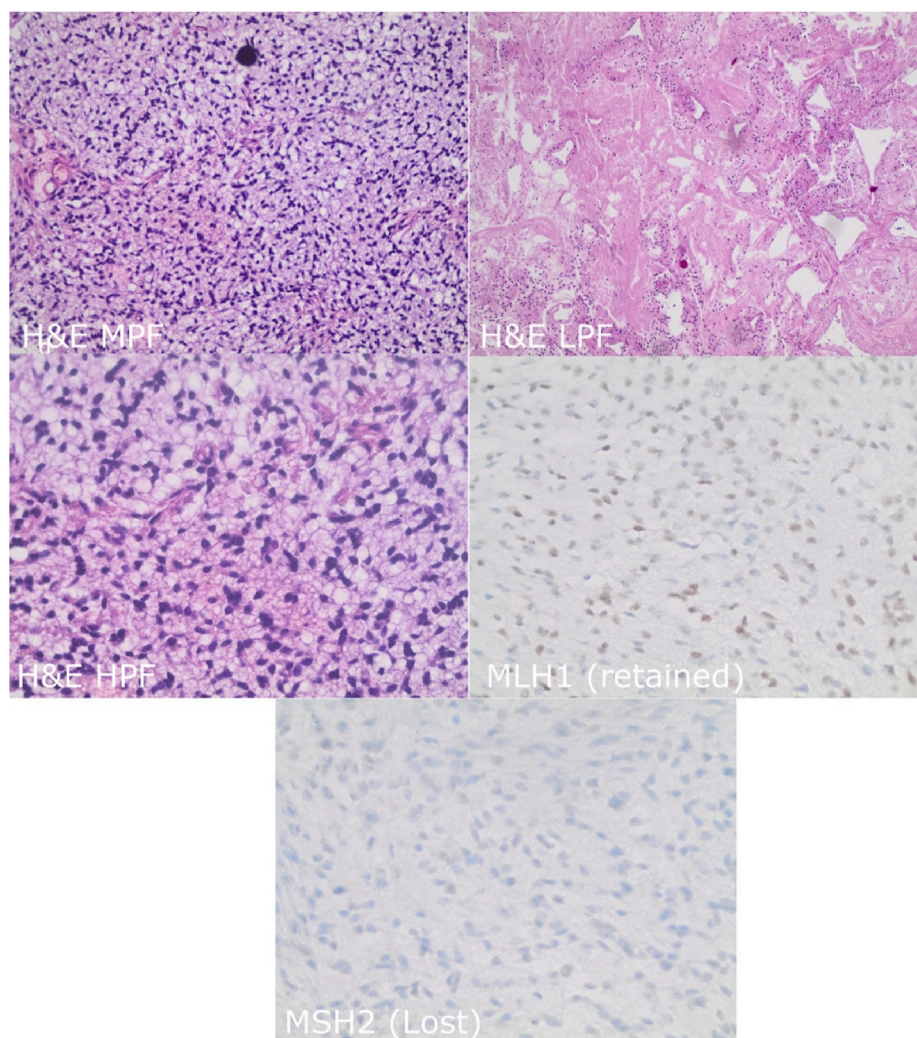
Fig. 3. The histopathology section indicating a malignant tumor. Immunohistochemistry showed tumor cells to be positive for GFAP and Vimentin, while negative CD31, CD 34, S100 and p53.

surgery, chemotherapy and radiotherapy. Unfortunately, mutation repair protein-deficient malignancies especially the high grade glioma were found to show strong resistance to chemotherapy used for ordinary high grade gliomas. Luckily, MMR-protein deficient high grade glioma were found to be responsive to Temozolimide and the new emerging

immunotherapy PD-1 inhibition which offer a new therapeutic avenue optimized for this entity of tumors [12,13].

Management of pediatric CNS tumors is quite challenge with tremendous burden of morbidity, risk of chemotoxicity and insufficient treatment dosing. According to a French cohort study 45% of patients





**Fig. 4.** H&E stains sections of high power (HPF) and medium power (MPF) show cellular glial tumor with scattered mitotic figures while the low power field (LPF) shows areas necrosis. The final diagnosis was high grade glioma most consistent with glioblastoma, WHO grade IV.

with CMMRD syndrome did not survive their first tumor; 50% of those patients had brain tumors [14]. thus Younger age of the first tumor and presence of high grade glioma have for worse prognosis and overall survival, 3-years overall survival for patient with CMMRD-related high grade glioma was 20.5% [3].

These numbers highlight the importance of implementing surveillance programs to early detect potential brain and colon tumors by brain MRI and colonoscopies respectively [15]. Since patients with CMMRD syndrome may respond better to early detection and management and thereby may improve their survival rates.

#### 4. Conclusions

We have presented a case of intramedullary lesion in the cervical spine C3–C7 in a patient with CMMRD syndrome. The patient went laminectomy and excisional biopsy. Subsequent immuno-histologic examination of the tumor confirmed high grade glioma most suggestive of GBM. This is the first reported case of this location in a CMMRD patient; which highlights the importance of screening, diagnosing and future surveilling protentional tumors.

#### Methods

This first in-human case report has been registered under Research

Registry unique identifying number (UIN): [researchregistry6689](https://www.researchregistry.com/record/researchregistry6689). This case has been reported in line with the SCARE 2020 criteria.

#### Ethical approval

It is not applicable.

#### Sources of funding

This study was not funded.

#### Author contribution

This work was carried out in collaboration between all authors. Authors SMJ and SSD designed the study. Author ISD and MD managed the literature searches, data collection and wrote the first draft of the manuscript. Author OFJ managed the literature searches and completed the final draft. All authors read and approved the final manuscript.

#### Research registration number

This first in-human case report has been registered under Research Registry unique identifying number (UIN): [researchregistry6689](https://www.researchregistry.com/record/researchregistry6689).

## Guarantor

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## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Declaration of competing interest

No conflict of interest to declare.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102263>.

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