Inherited malignant brain tumour: A case of constitutional mismatch repair deficiency

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SUMMARY

Constitutional Mismatch Repair Deficiency (CMMRD) is a cancer-predisposing syndrome with high morbidity and mortality caused by biallelic pathogenic variants in one of the mismatch repair genes resulting in a broad spectrum of early onset of malignancies. Here we report a case of CMMRD with homozygous variant in the MSH6 gene manifesting as medulloblastoma in a child, born to first-degree consanguineous. CMMRD associated skin change resembling Neurofibromatosis type 1, are concurrently observed. Familiarity with CMMRD clinical presentations for screening and early detection of its related malignancies, in families affected by this form of inherited germline mutation is of clinical importance.

INTRODUCTION

Childhood brain tumour is the second commonest type of cancer in individuals aged 0-24 years globally causing significant morbidity and mortality.[1] Based on the 10-year report of the Malaysia National Cancer Registry on the incidence of childhood cancer from the year 2007-2016, brain and central nervous system tumours are the second commonest tumours for the children between 0-14 years.[2] Majority of brain and other CNS tumours in children and adolescents are malignant (age-adjusted incidence of 3.55 per 100,000) while non-malignant brain and other CNS tumours are less common (age-adjusted incidence of 2.60 per 100,000).[3] Several brain tumours such as gliomas, medulloblastomas, and vestibular schwannomas are associated with tumour predisposition syndromes.[4] Among the predisposition syndromes, Constitutional Mismatch Repair Deficiency (CMMRD) is rare. CMMRD is a distinct condition caused by biallelic pathogenic variant in one of these mismatch repair (MMR) genes-*MLH1, MSH2, MSH6,* or *PMS2*. Children with this syndrome present with a broad spectrum of tumours including haematological, brain, and gastrointestinal tract tumours. They have dermatological findings such as café-au-lait macules (CALM), neurofibromas and axillary freckling commonly seen in children with NF-1.[5] Ash leaf macules can also be found in children with Tuberous sclerosis. Parental consanguinity significantly increases birth incidence from 1 in a million for untreated parents to 110 times higher in parents consanguineous.[7]

CASE PRESENTATION

An 8 year old boy of Indian descent, born to consanguineous parents initially presented to a tertiary hospital with occipital headaches for 2 weeks associated with episodes of daily morning vomiting, blurring and double vision. He subsequently developed right hemiparesis. His parents are first cousins- with 3 living children. Their deceased second son was diagnosed with T cell lymphoblastic lymphoma at 1½ years old who succumbed at 5½ years old due to disease relapse. Diagram 1 shows the pedigree chart of his family and the affected children. Physical examination of this boy was remarkable for several café-au-lait macules (CALM) and some ashleaf hypopigmented macules on the trunk. (Figure 1).

Computed Tomography (CT) scan of the brain showed faint hyperdense mass in the right posterior cranial fossa 3.9 x 3.8 x 3.2-cm causing acute obstructive hydrocephalus. An urgent ventriculoperitoneal (VP) shunt was inserted. MRI of the brain and spine, post-VP insertion showed a well-defined heterogeneous solid mass in the right cerebellum measuring 4.3 x 5 x 3.6-cm with restricted diffusion and cerebellar tonsil herniation of 1.1cm.

Right suboccipital craniotomy and tumour debulking was performed. Histopathological examination (HPE) confirmed the diagnosis of Large cell/ anaplastic medulloblastoma, SHH-activated and TP53 mutant (CNS WHO grade 4). Microscopically (Figure 3), the cells moderate nuclear pleomorphism, with large round to angulated nuclei, stippled chromatin, conspicuous nucleoli and moderate eosinophilic cytoplasm. Nuclear moulding and cell wrapping were also observed. The mitotic figures were brisk with high proliferative index (Ki67) of 80%. Intervening fibrous tissue was readily seen in the tumour but no typical nodular pattern was observed. No obvious rhabdoid cells or rosette patterns were encountered. The cells expressed Synaptophysin, CD56, YAP1, GAB1, p53-mutant, intact INI1, Fli1, NeuN and LIN28A as shown in Figure 4. They did not express GFAP, LCA, CD20, CD79 alpha, nuclear Beta-catenin and CD99.

He recovered well post-operatively with only right-sided intention tremor. However, repeat post-surgery MRI brain revealed significant residual tumour consisting of two

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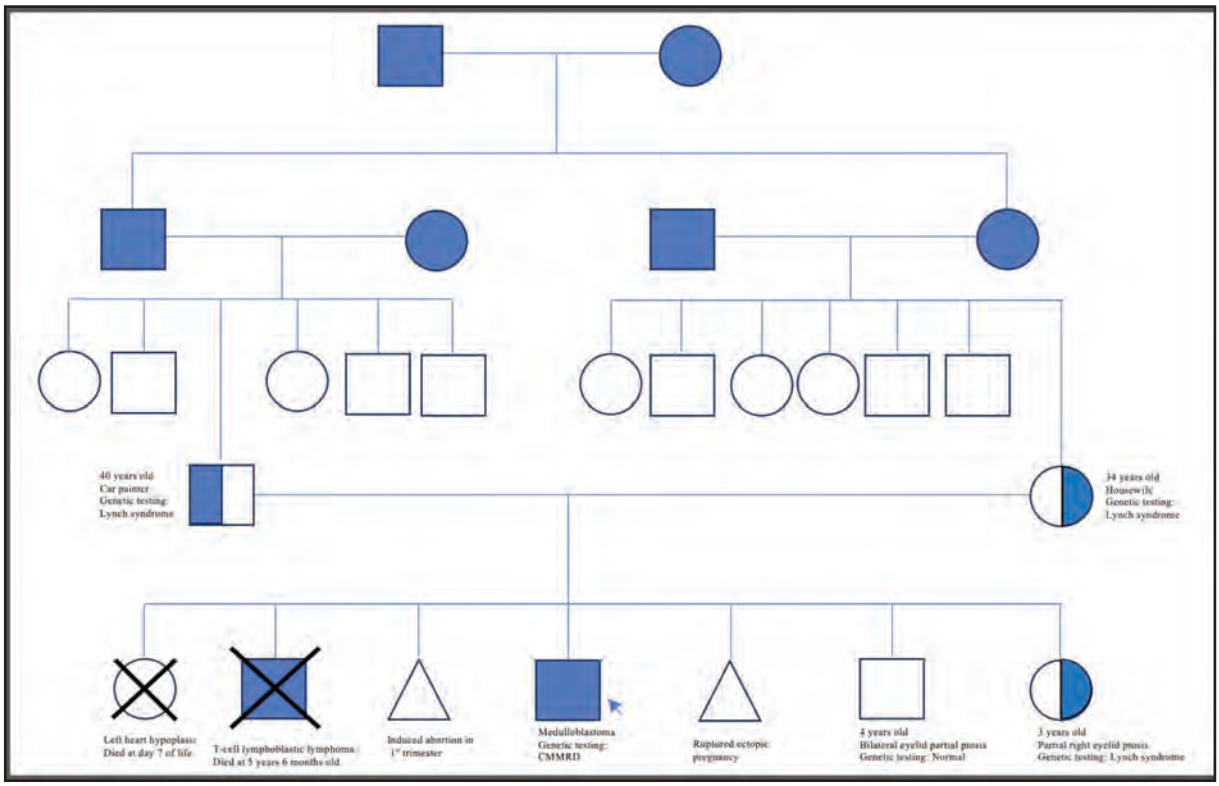

Diagram 1: Pedigree chart of the family.

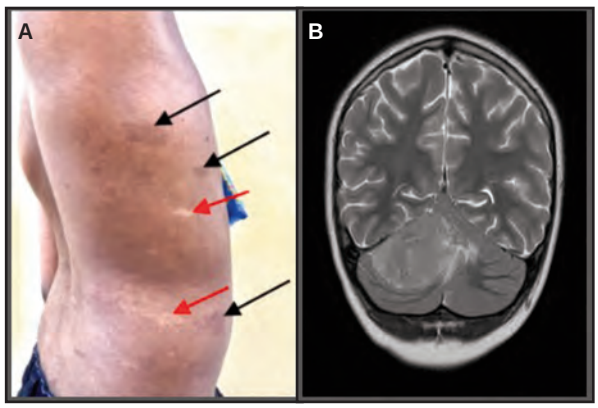

Fig. 1: Picture on the left (A) showing café au lait macules (black arrows) and ashleaf hypopigmented macules (red arrows) on the lumbar region. Picture on the right (B) shows the pre-op MRI brain (T1, T2 and T2 flare) showed a well-defined heterogeneous solid lesion (red arrow-head) in the right cerebellum with restricted diffusion and cerebellar tonsil herniation

Fig. 2: Picture A shows Haematoxylin and eosin (H&E) stain of the tumour cells of the posterior fossa tumour exhibiting moderate nuclear pleomorphism, with large round to angulated nuclei, stippled chromatin, conspicuous nucleoli and moderate eosinophilic cytoplasm. Nuclear moulding and cell wrapping were observed. Picture B and C shows Mismatch Repair (MMR) immunohistochemistry protein expression of neoplastic and non-neoplastic cells show loss of nuclear expression to MSH2 (B) and MSH6 (C)

enhancing masses at the right cerebellar resection bed, measuring 2.3 x 2.4 x 1.8-cm and 1.3 x 1.9 x 1.9-cm respectively. Posterior fossa craniectomy and tumour excision was performed. Gross total excision was achieved. Histomorphological findings were similar with the completion surgery.

Based on parental consanguinity, history of haematological malignancy in the sibling and skin pigmentary changes in the patient, cancer predisposition syndrome such as CMMRD syndrome was suspected. Hence immunohistochemistry (IHC) staining by Ventana for MMR proteins of MSH2, MSH6, MLH1 and PMS2 was performed as a screening using Benchmark ULTRA Ventana platform on the sections from formalin fixed paraffin embedded tumour specimen. This revealed a loss of MSH2 and MSH6 proteins in both the neoplastic and surrounding non-neoplastic cells (Figure 5). The sequencing analysis and deletion/duplication testing of 84 target genes from the combination of Invitae Multi-Cancer Panel and Invitae Common Hereditary Cancers Panel was performed on the patient's blood sample using Ilumina technology in Invitae Corporation. The results revealed homozygous pathogenic variant in MSH6 (c.3731T>G), affirming the diagnosis of CMMRD syndrome. Family screening was performed revealing both parents and a living younger sister having heterozygous pathogenic variant for the MSH6 variant gene confirming the diagnosis of Lynch syndrome.

Finally, a right frontal Ommaya reservoir was inserted and his left ventriculo-peritoneal shunt ligated for adjuvant intraventricular chemotherapy given concurrently with systemic chemotherapy.

DISCUSSION

The rarity of CMMRD and its diverse clinical manifestations pose both diagnostic and management challenges. According to literature, most cases of CMMRD (~60%) result from a mutation in Mismatch Repair Genes of *PMS2* followed by *MSH6*-(20–30% cases) and *MLH1/MSH2* genes-(10–20%).[8] MMR proteins recognize and repair mismatched nucleotide insertions or deletions during DNA replication. MMR deficiency facilitates the accumulation of genetic changes and consequently leads to the development of cancer.[7]

The tumour spectrum for this syndrome includes haematological malignancies, brain or central nervous system tumours, Lynch syndrome (LS)-associated tumours and other malignancies. LS-associated tumours include tumours from the colorectal, small bowel, endometrial, ureter[8], renal pelvis, biliary tract, stomach and bladder.[7] The initial age at diagnosis of CMMRD-related tumours is 0.4 to 39 years with 80% occurring before 18 years old.[7]. Wimmer et al., reported the median age of 9.5 years for brain tumours, 5 years for haematological malignancies, 16 years for LS-associated cancers. The mean age at first diagnosis of a malignancy is 9 years old. Individuals with CMMRD are known to be at high risk of developing a second malignancy at a later age usually during adulthood.

Brain tumours associated with CMMRD syndrome include high-grade gliomas, medulloblastomas and CNS embryonal tumours. In our case, the patient had Large cell/ anaplastic medulloblastoma, SHH-activated and *TP53* mutant (CNS WHO grade 4). Medulloblastoma, an embryonal tumour of the cerebellum is the most common malignant brain tumour in childhood. Most cases (95%) are sporadic in origin, with a few WNT medulloblastoma associated with Turcot syndrome and SHH medulloblastoma associated with Gorlin syndrome. In CMMRD syndrome the SHH signalling pathway is affected with a mutated *TP53* gene. Pathogenic variants DNA repair genes have been associated with medulloblastoma. In a study by Trubicka, J et al., six potentially new pathogenic variants were identified which included MSH2 (p.A733T and p.V606I), RAD50 (p.R1093*), FANCM (p.L694*), ERCC2 (p.R695C) and EXO1 (p.V738L). The same study provides preliminary evidence for a link between defects in DNA repair genes and treatment-related toxicity in children with medulloblastoma.

As mentioned earlier, CMMRD syndrome poses diagnostic challenges, as it often overlooked or undiagnosed; partly due to a lack of awareness among clinicians. In 2013, the European consortium 'Care for CMMRD' (C4CMMRD) proposed a three-point scoring system that should trigger diagnostic evaluation of CMMRD syndrome.[6]

Typically, immunohistochemistry (IHC) staining is used as a screening tool followed by germline mutation analysis for confirmation of CMMRD. However, due to limited availability of germline testing, IHC of MMR proteins is proposed as an ancillary diagnostic test for CMMRD.[7] To confirm CMMRD by IHC, loss of MMR expression in all cells of the investigated tissue (neoplastic and non-neoplastic cells) should be observed. In general, a truncating mutation in *PMS2* or *MSH6* will result in isolated loss of these proteins, whereas a mutation in *MLH1* or *MSH2* will lead to concurrent loss of MLH1/PMS2 or MSH2/MSH6 protein expressions respectively, since *MLH1* and *MSH2* are obligatory partners in the formation of MLH1/PMS2 and MSH2/MSH6 heterodimers.[7]

In 2021, a set of diagnostic criteria consisting of MMR germline results, ancillary test and clinical manifestations was recommended by C4CMMRD consortium. Ancillary tests include assays showing microsatellite instability (MSI) in constitutional tissue[6], functional assays showing loss of MMR activity and MMR immunohistochemistry (IHC) showing loss of MMR protein expression. Patient who fulfil the diagnostic criteria warrants CMMRD surveillance.

Besides tumours, CMMRD patients often have café-au-lait macules (CALM). They may also have neurofibromas and axillary freckling[7]. Most of these patients have multiple (two or more) CALMs-but they do not always have ≥6 CALM

needed for diagnosis of Neurofibromatosis Type 1 (NF1). A study suggested that CALM in CMMRD could be distinguished from CALM in NF1 by experienced physicians through the degree of pigmentation and shape.[8] It has been hypothesised that NF1 gene is a frequent somatic target in CMMRD.[7]

Genetic counselling should be offered to parents before germline testing of the affected child, including information on potential risk of recurrence and consequences of heterozygous mutation in both parents. Predictive testing should be offered to all family members once a mutation has been identified. The family must be informed of the potential therapeutic implications and of the high risk of second malignancy if the patient is positive. Preferentially, targeted gene mutation analysis is performed. In cases where tumour tissue is not available for IHC analysis or the results are inconclusive, mutation analysis of blood samples by genetic sequencing method can also be considered.[8]

Monitoring patients with CMMRD presents a formidable challenge due to the broad spectrum of associated malignancies.[9] Developing a specific surveillance protocol is particularly daunting given this complexity. Nevertheless, once an early diagnosis of CMMRD is confirmed, regular and vigilant screening becomes imperative to detect other CMMRD-related malignancies. This surveillance protocol should encompass a rigorous clinical evaluation, including a full blood count and monitoring of carcinoembryonic antigen (CEA) levels. Additionally, MRI of the brain, lower gastrointestinal endoscopy, and transvaginal ultrasound for endometrial and ovarian cancers should be integral components of this comprehensive screening approach. Implementing such a proactive strategy is paramount for the early detection and management of potential malignancies. Accurate and early diagnosis of CMMRD has important implications in the management of the patients and their families. Clinicians should consider conducting IHC staining of MMR proteins and gene analysis in children with brain tumors and presents with clinical criteria as mentioned above. An accurate diagnosis is pre-requisite for surveillance and improved survival for patients and their families.

CONCLUSION

Navigating the intricacies of Constitutional Mismatch Repair Deficiency (CMMRD) syndrome demands a proactive and multidisciplinary approach. This rare syndrome, characterized by its diverse clinical manifestations driven by mutations in Mismatch Repair (MMR) genes, underscores the critical need for early and precise diagnosis. Despite the challenges posed by the syndrome's rarity and the wide spectrum of associated malignancies, diligent surveillance is paramount. By implementing these strategies, we can optimize the management and surveillance of CMMRD, significantly enhancing patient outcomes. With its unique presentation, including but not limited to skin abnormalities, brain tumors, and haematological malignancies, CMMRD requires a comprehensive and tailored approach. This approach not only improves patient care but also contributes to the growing body of knowledge surrounding this complex syndrome, fostering advancements in its understanding and treatment.

DISCLOSURE

Consent was obtained from the patient's parents for this study. All authors contributed to manuscript drafting. All authors read and approved the final manuscript. The authors declare no conflict of interest.

ETHICAL APPROVAL

The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has deemed that this study does not require ethical approval.

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REFERENCES

1. Raja N, Hayes L, Basta N, McNally RJQ. International trends in the incidence of brain tumours in children and young-adults and their association with indicators of economic development. Cancer Epidemiology. 2021; 74: 102006.
2. Raman, S. Et Al. (Eds) (2021) The Incidence Of Childhood Cancer In Malaysia 2007-2016. Institut Kanser Negara, Putrajaya.
3. Farouk Sait S, Walsh MF, Karajannis MA. Genetic syndromes predisposing to pediatric brain tumors. Neuro-Oncology Practice. 2021; 8(4): 375-90.
4. Wimmer K, Etzler J. Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg? Human Genetics. 2008; 124(2): 105-22.
5. Wang Q, Montmain G, Ruano E, Upadhyaya M, Dudley S, Liskay RM, et al. Neurofibromatosis type 1 gene as a mutational target in a mismatch repair-deficient cell type. Human genetics [Internet]. 2003; 112(2): 117-23.
6. Abedalthagafi M. Constitutional mismatch repair-deficiency: current problems and emerging therapeutic strategies. Oncotarget [Internet]. 2018; 9(83).
7. Wimmer K, Rosenbaum T, Messiaen L. Connections between constitutional mismatch repair deficiency syndrome and neurofibromatosis type 1. Clinical Genetics. 2017 Jan 10; 91(4): 507-19.
8. González-Acosta M, Marín F, Puliafito B, Bonifaci N, Fernández A, Navarro M, et al. High-sensitivity microsatellite instability assessment for the detection of mismatch repair defects in normal tissue of biallelic germline mismatch repair mutation carriers. Journal of Medical Genetics [Internet]. 2020 Apr 1 [cited 2024 Jan 26]; 57(4): 269-73.
9. Sameen Bin Naeem, Ullah N, Mussadique Ali Jhatial, S. Mudassar Muzaffar, Abbas M, Iftikhar IH, et al. Constitutional Mismatch Repair Deficiency (CMMRD) Syndrome: A Case Report of a Patient With Multiple Metachronous Malignancies. Cureus. 2023;.
10. Trubicka J, Żemojtel T, Hecht J, Falana K, Piekutowska-Abramczuk D, Płoski R, et al. The germline variants in DNA repair genes in pediatric medulloblastoma: a challenge for current therapeutic strategies. BMC Cancer. 2017; 17(1).