A Case of Constitutional Mismatch Repair Deficiency (CMMRD)*

Ma. Janina T. Layosa, MD[1]; Julieta Rita Gonzales-Santos, MD, DPPS, DPSHBT, FPSPO, DPSP[2]

ABSTRACT

Constitutional mismatch repair deficiency (CMMRD) is a hereditary predisposition of malignancy evident in childhood leukemias, lymphomas, and malignant tumors of the brain, GI tract. It is a very rare condition that affects 1 per 1 million patients. Patients with CMMRD syndrome may also manifest with Neurofibromatosis Type 1 (NF1) phenotypic features, and benign masses, particularly in the gastrointestinal tract.This is a case of a 12-year old male who presented with phenotypic features of NF1, developed Acute Lymphoblastic Leukemia at 7 years old and went into remission. He subsequently developed synchronous Glioblastoma and Poorly differentiated Adenocarcinoma of the rectum.This report aims to raise awareness regarding the possibility of a CMMRD syndrome in pediatric patients who present with phenotypic features of NF1, and in those patients who present with two or more malignancies in their lifetime.

Keywords: *Constitutional mismatch repair deficiency (CMMRD), Glioblastoma Multiforme, Acute lymphoblastic leukemia, metachronous cancers, synchronous cancers*

INTRODUCTION

Constitutional Mismatch Repair Deficiency (CMMRD), also known as Biallelic Mismatch Repair deficiency (BMMRD) is a rare and aggressive autosomal recessive disorder linked with the predisposition of a child to develop synchronous or metachronous malignancies such as childhood leukemias, lymphomas, and malignant tumors. Aside from malignancies and hereditary involvement, patients with CMMRD also manifest with phenotypic features suggestive of neurofibromatosis type 1 (NF1)[1]. CMMRD is a hereditary predisposition of malignancy which manifest from infancy up to young adulthood, with an incidence of one per 1 million patients worldwide. In CMMRD, mismatch repair genes such as mutS homolog 2 (MSH2), mutL homolog 1 (MLH1), mutS homolog 6 (MSH6), and post-meiotic segregation increased 2 (PMS2)are mutated. These mismatch repair genes are responsible for genetic stability and for repair of errors during DNA replication. Most patients diagnosed with CMMRD have mutations in PMS2 or MSH6 genes, and these mutations can lead to more malignancies. However, due to lack of specific clinical features of CMMRD, it causes delay in diagnosis, and worse, may not be diagnosed at all[1][2][3].

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

***2nd Place, 29th Philippine Medical Association Case Report Presentation, May 16, 2023**

[1]Resident, Department of Pediatrics, De La Salle University Medical Center, Cavite

[2]Advisor

CASE REPORT

This is the case of a 12-year-old male with phenotypic features of NF1 (multiple café au lait macules on the face, trunk, arms, legs and buttocks; axillary freckling; 1.5 x 1.5 cm firm non-tender, non-movable mass on the left antecubital fossa), who was diagnosed with Acute Lymphoblastic Leukemia, B-Cell Average Risk in December 2017. He initially presented with pallor, fever, and joint pains. He was treated with COG AALL0232 protocol until February 2021, with exit BMA done in March 2021 which showed a marrow in remission. Additional skin lesions include several hypopigmented spots on his face, trunk, arms, and legs.

There is a history of consanguinity: the Father's grandfather and the Mother's great-aunt were first degree cousins.Family medical history revealed colorectal cancer (grandfather), and Neurofibromatosis 1 (aunt who is 2nd/3rd degree cousin of both his parents).

In March 2022, he presented with headache and vomiting, with no neurologic deficits. Cranial MRI with IV contrast revealed mildly lobulated, intra-axial lesion measuring 30.3 x 25.2 x 25.0mm (AP x T x CC) along the cortical-subcortical region of the left frontal lobe at the level of corona radiata. He underwent craniotomy and gross total excision of tumor. Intraoperative findings revealed a 2x3cm mass at left frontal lobe with invasion of surrounding brain parenchyma. Histopathological examination revealed High Grade Round Cell Malignancy. Immunohistochemistry were negative for TDT, CD3, and CD79a, but positive for GFAP, and IDH1 which support the diagnosis of Glioblastoma. Further testing for CMMRD on the brain tumor was done which revealed: P53 mutant pattern (IHC), ATRX lost (IHC), MSH2 and MSH6: retained; PMS2 lost in tumor cells and normal cells (CMMRD pattern), MLH1 lost in most cells, PDL1 negative, CD8 32/mm2 plus perivascular lymphocytes. Impression: Glioblastoma, IDH-wildtype. Genotype is still pending. The patient underwent radiotherapy with 54 Gy in 33 fractions, with concurrent chemotherapy with CCNU. During RT, he presented with headache, a repeat MRI done in June 2022 revealed that the previously described heterogeneously enhancing, mildly lobulated, intra-axial lesion in the left frontal lobe at the level of corona radiata was no longer visualized. But an ill to fairly defined avidly enhancing region is seen around the excision site in the left frontal lobe, with the presence of extensive vasogenic edema. This was read as possible post-RT changes vs tumor recurrence, and imaging after 3 months was suggested.

He was supposed to undergo 6 more cycles of maintenance chemotherapy with CCNU every 42 days. A repeat cranial MRI with IV contrast done post RT revealed slight increase in the size of the previously described avidly enhancing region around the excision site in the left frontal lobe, now measuring approximately 38.75 x 35.39 x 30.23 mm, with the internal component of exhibiting heterogeneity compared with the prior study. There is also progression of vasogenic edema with associated effacement of the adjacent sulci as well as interval increase in the degree of compression of the left lateral ventricle and rightward shifting of the midline structures now measuring about 10.31 mm (previously 8.30 mm).

1 week prior to his first maintenance chemotherapy, he presented with painless, hematochezia not associated with fever, abdominal pain, diarrhea, or constipation. He underwent esophagogastroduodenoscopy (EGD) and colonoscopy with biopsy. EGD findings were unremarkable, however colonoscopy findings revealed colonic polyp, sigmoid colon, 0-IIa, JNET type 2A, and rectal new growth, probably malignant. CEA was elevated with a value of 8.47 ng/mL. Histopathologic findings then revealed

poorly differentiated adenocarcinoma of the rectum. Abdominal MRI and PET-CT scan revealed a 3.2 x 1.8 x 3.6 cm hypermetabolic heterogeneously enhancing soft tissue mass in the right side of the rectum, with at least 6 Hypermetabolic subcentimeter to marginal sized interiliac and mesorectal lymph nodes, more on the right, likely representing metastases. The PET-CT also revealed the presence of a 3.6 x 4 cm heterogeneously enhancing mass in the left frontal lobe with surrounding edema, which has decreased FDG uptake, corresponding to glioblastoma recurrence.

As of writing, present working impression is: Constitutional Mismatch Repair Deficiency Syndrome: Poorly Differentiated Adenocarcinoma, rectum stage III; Glioblastoma, IHC-wildtype, S/P craniotomy and excision (March 2022), S/P concurrent chemotherapy-radiotherapy (August 2022) with tumor recurrence; ALL, B-cell, average risk S/P chemotherapy (Feb 2021) in remission. Because of the simultaneous occurrence of 2 primaries, plan is to give Immunotherapy with Pembrolizumab at 2 mg/kg every 21 days.

DISCUSSION

Here is a patient with phenotypic features of NF1, hypopigmented spots on the skin, with a history of consanguinity, who was diagnosed with acute lymphoblastic leukemia at the age of 7 years old, then developed synchronous Glioblastoma and Poorly differentiated adenocarcinoma of the rectum at 12 years old.

Development of second primary neoplasms is often multifactorial. Main risk factors include genetic and/or host predisposition in developing multiple malignancies[4]. Involvement of different malignancies in childhood may be attributed to a genetic defect called Constitutional mismatch repair deficiency, which is a rare autosomal recessive disease. It is a hereditary cancer predisposition in infancy or young adulthood caused by mutations in DNA mismatch repair (MMR) genes. MMR genes are responsible for eliminating mismatch of base to base deletions and insertions resulting from errors of DNA polymerase during DNA synthesis. These genes are specifically mutS homolog 2 (MSH2), mutL homolog 1 (MLH1), mutS homolog 6 (MSH6), and post-meiotic segregation increased 2 (PMS2); they are responsible for stabilization of genomes for error correction and apoptosis when damage to DNA ensue. Heterozygous (monoallelic) mutations in MMR genes affecting functionality of MMR may cause Lynch Syndrome (LS), formerly known as hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Identification of germline mutations in at least one of the repair genes is necessary for the definition of LS. On the other hand, CMMRD is brought on by Constitutional germline mutations in the LS-causing MMR genes[1][5]. The hallmark of CMMRD is an early onset of cancer, with a median age of 7[3].

Children with malignancies linked to CMMRD may not have a family history of Lynch-associated cancers but should nonetheless be tested for MMR gene abnormalities The index case of CMMRD frequently lacks family history of cancers that would raise suspicion of the syndrome. Delays in diagnosis of BMRRD may be attributed to its complex nature, to be specific the lack of clear disease-specific clinical features covering the full spectrum of tumors associated with CMMRD, as well as diagnostic difficulties[1][5].

Data from the International Replication Repair Deficiency (IRRD) Consortium showed 193 tumors in 110 patients diagnosed with CMMRD. Brain tumors (High grade gliomas, medulloblastomas and CNS embryonal tumors) constitute 44%, GI cancers (most common of which are the colorectal carcinomas) constitute 27%, and

hematologic malignancies (most commonly Non-Hodgkin lymphomas, but also leukemias) constitute 19% of the tumors detected. Other malignancies include sarcomas, skin cancer, breast cancer, Wilm's and other kidney cancers, bladder cancers, retinoblastoma, neuroblastoma, ovarian, endometrial, and prostate cancers.[6] Up to 25% of patients present with synchronous (diagnosed at the same time, or within 6 months of each other[7]) malignancies. [8]

Due to lack of clear disease-specific clinical features of CMMRD, the European consortium created criteria called "Care for CMMRD (C4CMMRD)" which is a scoring system that has high sensitivity for CMMRD and can help for further genetic testing and counseling. Table 1 shows the C4CMMRD scoring system, and a score of 3 points and higher is highly suggestive of CMMRD[1][3] Patients have this score should undergo further testing for CMMRD.

Indications for CMMRD-Testing	More than 3 points
Maligancies or pre-malignancies: one is mandatory. If more than one is present add points	
LS carcinoma at age less than 25 years	3 points
Multiple bowel adenomas at age less than 25 years and absence of APC/MUTYH or a single grade dysplasic adenoma (also at age less than 25 years).	3 points
WHO grade III or IV glioma at age less than 25 years	2 points
NHL of T-cell lineage or sPNET at age less than 18 years	2 points
Any malignancy in a patient under 18 years	1 point
Additional features: if more than one of the following are present add points	
Clinical NF1 diagnosis or more than 2 hyper/hypo-skin pigmentations (greater than 1 cm)	2 points
Diagnosis of LS in a 1st and/or 2nd degree relative	2 points
LS carcinoma, high grade glioma, sPNET, or NHL	1 point
Sibling with a childhood cancer	1 point
Multiple pilomatricomas present	2 points
One pilomatricoma present	1 point
Agenesis of the corpus callosum or non-therapy induced cavernoma	1 point
Consanguineous parents	1 point
Deficiency/reduced levels of IgG2/4 and or IgA	1 point

Table 1. Diagnostic scoring criteria for CMMRD from the European consortium

"Care for CMMRD"

Our patient has fulfilled several criteria including the following:1) LS carcinoma at age less than 25 years (3 points); 2)presence of WHO Grade IV Glioma at age less than 25 years old (2 points); 3) malignancy (having acute lymphoblastic leukemia) under 18 years of age (1 point); 4) clinical NF1 diagnosis of more than 2 hyperpigmented skin lesions (2 points); and 5) consanguineous parents (1 point), all corresponding to 9 points, which is highly suggestive of CMMRD.

Microsatellite instability (MSI) and immunohistochemistry (IHC) analysis, followed by mutation analysis, are typically used to confirm the diagnosis. IHC is a helpful technique used in patients with CMMRD associated neoplasms

including brain tumors and directs subsequent mutation analysis in the four MMR-genes. The patient underwent IHC analysis, which revealed loss of MLH1 and PMS2, hence strongly supporting our diagnosis. Patients with CMMRD with mutations in PMS2, as well as MSH6 are at risk of developing more than one malignancy[3]. In the case of our patient, he had acute lymphoblastic leukemia now in remission, high grade glioma, and rectaladenocarcinoma. MSI analysis follows current protocols used for LS-screening, but this analysis may be unreliable in CMMRD related brain tumors[2][9].

The International Replication Repair Deficiency (IRRD) Consortium published the CMMRD Diagnostic Criteria (Table 2). Our patient has hallmark CMMRD cancer on diagnosis, 1 positive ancillary test (MMR immunohistochemistry), and family history of consanguinity, with pending genotyping.At the moment, the patient is considered to have a Likely Diagnosis. Patients with Definite and Likely Diagnosis of CMMRD should undergo CMMRD surveillance as per published guidelines.[10]

CRITERION		GERMLINE RESULT *PMS2, MSH6, MSH2, MLH1*	POSITIVE ANCILLARY TESTING	CLINICAL PHENOTYPE
Definitive Diagnosis (Strong Evidence Of CMMRD)	1	Biallelic pathogenic variants (P/P), confirmed in trans	Not required unless unaffected >25 yrs, then one required	Not required if under age 25 (if no malignancy over age 25, ancillary testing required)
	2	Biallelic P/LP or LP/LP variants, confirmed in trans	One required unless unaffected by hallmark cancer, then 2 required	Hallmark CMMRD cancer diagnosis> or C4CMMRD criteria of 3 points (then 2 ancillary tests required)
	3	Heterozygous P or LP variant (+/- VUS or likely benign variants)	One required	Hallmark CMMRD cancer diagnosis
	4	No P or LP MMR variants (including VUS/VUS) or No testing available (i.e. deceased proband)	Two required	Hallmark CMMRD cancer diagnosis
Likely Diagnosis (Moderate evidence of CMMRD)	5	Biallelic P/LP or 5 LP/LP variants confirmed in trans	Not required	C4CMMRD criteria of 3 points
	6	Heterozygous P or LP variant or no testing available (i.e. deceased proband)	Two required	a. C4CMMRD criteria of 3 points b.Individual< age 18 with NF1 features (i.e. no malignancy or polyposis history polyposis history) c. Malignancy under age 30

Table 2. CMMRD Diagnostic Criteria, from International Replication Repair

Deficiency (IRRD) Consortium

Patients diagnosed with CMMRD have a median survival of 30 months from the time the primary tumor is diagnosed[1]. However, surveillance seems to have an impact on survival as shown in the IRRD consortium data where patients who were undergoing full surveillance had significantly better 4-year OS rates of 79% compared to those who underwent partial surveillance 55% survival, and no surveillance (15%) They also reported the high likelihood of transformation of low to high grade cancers among these patients.[6]

Surveillance of CMMRD must be done from the time of diagnosis. The latest published guidelines include: Brain MRI at diagnosis and every 6 months for brain tumors; Whole body MRI to start at 6 years and once a year for all tumors; CBC to start at 1 year old and every 6 months for leukemias; Abdominal ultrasound to start at 1 year old and every 6 months for lymphomas; Upper GI endosocopy, Visual Capsule Endoscopy and Ileocolonoscopy to start at 4-6 years at least once a year but increases once polyps are found; and GYN exam, transV ultrasound to start at 20 years old and once yearly after that to look for GYN malignancies It was noted that malignancies that were detected asymptomatically had better survival rates than those that were detected symptomatically.[10]

Aside from testing the affected child, the parents should also get genetic counseling that explains the clinical repercussions of a likely heterozygous mutation in both parents as well as the potential 25% probability of recurrence. Once a mutation has been discovered, predictive testing should be made available to all family members in accordance with the established interdisciplinary counseling guidelines. Determining recommendations for surveillance of affected patients is difficult due to the vast range of malignancies in CMMRD patients. The likelihood of finding related cancers, such as colon cancer or brain tumors, at an operable stage may be increased by early detection of CMMRD and subsequent cancer screening at regular intervals[2]. In our case, patient's siblings who also has CALM, is advised to have a skin biopsy for IHC and genetic testing.

The ideal course of treatment for patients with CMMRD is not currently known. Several papers emphasize that special consideration should be given to the high risk of a second malignancy, the potential for greater cytotoxicity and decreased efficacy of chemotherapeutic drugs due to constitutionally deficient mutation repair[2]. Several commonly used chemotherapeutic drugs need a functioning MMR system to cause tumor destruction. MMR-deficient cells typically exhibit chemotherapy resistance with mercaptopurine and temozolomide, which are frequently used to treat glioma and hematological malignancies, respectively. MMR resistance is shown by temozolomide, the medication of choice for glioblastomas multiforme, a highly aggressive CMMRD-brain tumor. Since temozolomide is known to promote the accumulation of somatic mutations in patients, increasing the risk of subsequent tumors, its usage is now avoided in GBM associated with CMMRD. However, effective chemotherapeutic therapy for CMMRD cancer are still scarce, and novel effective medicines are urgently needed. No clear lack of efficacy of other therapeutic agents, such as alkylating agents, has been found.

There has now been a development of immunotherapies termed checkpoint inhibitors which counteract the actions of proteins that hamper the immune response to cancer. PD-L1 serves as a binding site for PD1 and is over expressed in several malignancies. When PD1 binds to PD-L1 inside the tumor, PD1 signaling is activated, which inhibits T cell activation and enables the tumor to resist immunological attack. Enhancing the anti-cancer T cell response and fostering anti-tumor activity can be achieved by inhibiting the interaction of PD1 and PD-L1. In CMMRD cancers, inhibiting PD-1 results in a significant clinical response, and CMMRD tumors respond to PD-1 blockers better than MMR-competent tumors. Children with CMMRD and recurrent GBM who were treated with PD1-blockers demonstrate tumor reduction in MRI scans, indicating a satisfactory therapeutic response. Immune-based therapies have been found to be efficacious in CMMRD related tumors, hence may prolong survival[1][10].

CONCLUSION

Because of its rarity and complexity, Constitutional Mismatch Repair Syndrome is often unrecognized and under diagnosed. Because these cases are rare and few have been reported, encountering a patient with this disease may pose diagnostic and therapeutic dilemmas. A high index of suspicion is needed for clinicians to be able to recognize this disease. We therefore encourage physicians who encounter pediatric patients with phenotypic features of NF1 to be more vigilant in obtaining detailed family histories of cancer or consanguinity, because early detection of the disease leads to surveillance, which can significantly alter the patient's survival.

REFERENCES

1. Abedalthagafi, M. (2018). Constitutional mismatch repair-deficiency: current problems and emerging therapeutic strategies. *Oncotarget Vol 9 (No 83)*, 35458-35469.
2. Wimmer, K., & Kratz, C. P. (2010). Constitutional mismatch repair-deficiency syndrome. *Haematologica, Vol 95(5)*, 700-701.
3. Tabori, U., & Hansford, J. R. (2017). Clinical Management and Tumor Surveillance Recommendations of Inherited Mismatch Repair Deficiency in Childhood. *Clinical Cancer Research*, 32-37.
4. Yamanaka, R., & Hayano, A. (2016). Secondary glioma following acute lymphocytic leukemia: therapeutic implications. *Neurosurgical Review*, 549–557.
5. Lobbous, M., Bernstock, J. D., Coffee, E., Friedman, G. K., Metrock, L. K., Chagoya, G., . . . Nabors, L. B. (2020). An Update on Neurofibromatosis Type 1-Associated Gliomas. *Cancers*, 1-15.
6. Durno, C., & et.al. (2021). Survival Benefit for Individuals With Constitutional Mismatch Repair Deficiency Undergoing Surveillance. *Journal of Clinical Oncology, 39 (51)*, 2779-2790.
7. Aronson, M., Colas, C., Shuen, A., Hampel, H., Foulkes, W. D., & al, e. (2021). Diagnostic criteria for constitutional mismatch repair deficiency (CMMRD): Recommendations from the international consensus working group. *Journal of Medical Gene.*
8. N, T., Dokmetzioglou, J., Giannoulis, K., Kesisoglou, I., Sapalidis, K., Kotidis, E., & Gambros, O. (July 2008). . Synchronous and metachronous adenocarcinomas of the large intestine. *Hippokratia, 12 (3)*, 150-152.
9. RANA, H. Q., & SYNGAL, S. (2017). Biallelic Mismatch Repair Deficiency: Management and Prevention of a Devastating Manifestation of the Lynch Syndrome. *Gastroenterology (Vol 152)*, 1254–1257.
10. Henderson, J. J., & et.al. (2022). Immune Checkpoint Inhibitors as Single Therapy for Synchronous Cancers Exhibiting Hypermutation: An IRRDC Study. *JCO Precision Oncology*.