

CASE REPORT

10-YEAR-OLD PAKISTANI BOY WITH MULTIPLE MALIGNANCIES: LOSS OF PMS2–CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY

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Constitutional Mismatch repair deficiency (CMMRD) is a cancer predisposition syndrome. Four main common malignancies seen are, haematological, brain tumours, colorectal cancers, and intestinal polyps. We are reporting a 10-year-old boy with CMMRD; diagnosed with hematological malignancies, followed by low grade glioma in thalamus. There was loss of PMS2, whereas immunostaining was retained for MLH1, MSH2 and MSH6. Early diagnosis of CMMRD is crucial especially in countries like Pakistan, where consanguineous marriages are common. Increasing awareness among the physicians will help in early diagnosis, surveillance and in providing appropriate genetic counselling to the family.

Keywords: Acute leukaemia; Mismatch Repair Deficiency; PMS2.

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INTRODUCTION

Constitutional mismatch repair deficiency (CMMRD) is a cancer predisposition syndrome that presents mainly during childhood or in young adults. The clinical presentation of CMMRD is variable, patients commonly present with brain tumours, haematological malignancies like leukaemia or lymphoma, or colorectal tumours.¹ CMMRD occur due to mutations in the specified mismatch repair genes, mutS homolog 2 (MSH 2), mut L homolog (MLH 1), mut S homolog 6 (MSH 6), post meiotic segregation increase 2 (PMS2) and post meiotic segregation increase 1 (PMS 1).² We present a 10-year-old boy who was diagnosed with CMMRD, after taking approval from Institutional Review Board (EX-22-07-20-04) and informed consent from the parents.

CASE DISCUSSION

A 10-year-old male child presented to Shaukat Khanum Memorial Cancer Hospital and Research Centre in 2014

with complaints of fever, petechiae and bruises for the past one month. Parents had consanguineous marriage; family history (maternal cousin) was positive for brain tumours. He had cervical and axillary lymphadenopathy, along with multiple café-au-lait spots with the largest measuring about 2 cm in size. He had hepatosplenomegaly; liver was palpable 4 cm below the right costal margin, with the total span of 13 cm, whereas spleen was palpable 3 cm below the left costal margin. Complete blood count with peripheral smear revealed leucocytosis and thrombocytopenia with 35% blast cells. On flow cytometry CD 10-, CD -20, CD-45, HLA-DR, Tdt were positive, diagnosed as precursor B cell acute lymphoblastic leukemia and was started on United Kingdom acute lymphoblastic leukaemia-2011 (UKALL) protocol-based chemotherapy. In December 2017 child again presented with subacute intestinal obstruction and CT scan revealed heterogeneously enhancing lesion in left hemi abdomen (Figure-1).

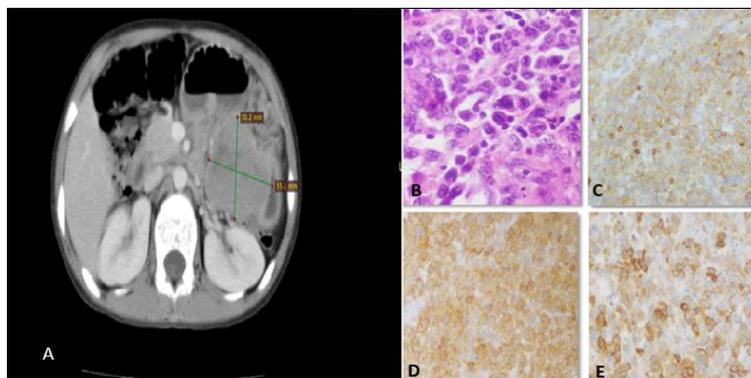


Figure-1:(A) heterogeneously enhancing lesion measuring 55×50 mm in left hemi abdomen at the level of renal hilum and surrounding bowel wall thickening. (B) Pleomorphic large cells with irregular nucleoli. (C) LCA positive. (D) CD 163 positive. (E) CD 4 positive

Resection was done and histopathology revealed, neoplasm composed of diffuse non-cohesive pleomorphic large cells with irregular nuclei and prominent nucleoli. Multinucleated large cells with brisk mitotic activity was noted, Ki 67 showed 60% proliferation. LCA, CD-163, CD-4, lysozyme was positive and was diagnosed with histiocytic sarcoma. He was treated on intensive chemotherapy protocol based on cytarabine, etoposide and daunorubicin (ADE) followed by high dose cytarabine (HiDac).

Keeping in view his positive family history further analysis was done to rule out tumour predisposition syndromes. Immunohistochemistry (IHC) for mismatch repair proteins was performed (at outside facility); there was loss of immunostaining for PMS2, whereas immunostaining was retained for MLH1, MSH2, MSH6, and hence suggesting Constitutional Mismatch Repair Deficiency (CMMRD).

In May 2018, the child started having complaints of headache on off, MRI brain was done. On T2FLAIR images, there was high signal intensity in the pulvinar of the right thalamus and was seen bulging into the right lateral ventricle. On MR spectroscopy there was increased uptake of choline as compared to NAA, NAA/choline ratio was 0.62, choline/creatinine ratio was 1.64, NAA value is 2.02, creatinine was 3.04, and lipid and lactate were low. The child was diagnosed with low grade glioma in thalamus. In November 2018, the child had relapsed histiocytic sarcoma, but no further therapy was offered. He died in May 2019 cause of disease burden. Further analysis for gene mutations was offered to the family but the parents refused.

DISCUSSION

The mismatch repair (MMR) machinery contributes to the genomic integrity; MMR corrects single base pair mismatches and small insertion-deletion loops that arise during replication. Monoallelic mutations in the MMR gene can result in the cancer predisposition condition known as lynch syndrome (LS), whereas Biallelic mutations result in CMMRD. Individuals with CMMRD develop multiple malignancies in their childhood, rarely reaching adulthood.³ The cancer presentation of CMMRD depends on the genes mutated, patients with MSH6 and PMS2 mutations often get brain tumours within 10 years of life and patients with PMS2 mutations develop secondary malignancies.⁴ In CMMRD MLH1/MSH2 mutations has the worse prognosis, whereas MSH6 or PMS2 have complications due

to secondary malignancy, which was the same as in our case.

Individuals with CMMRD have grim prognosis, the most common malignancy seen among them are brain gliomas followed by non-Hodgkin lymphoma and colorectal carcinomas. Given the natural history of CMMRD, rapid diagnosis is always difficult; hence European Consortium has developed a rapid scoring system, "Care for CMMRD" based on clinical criteria for the rapid detection.⁵ In our case neither of the parents had a history of malignancy making the diagnosis even more difficult.

Chemotherapeutic agents need functional MMR genes to imitate tumour damage; MMR deficient cells are resistant to chemotherapeutic agents, rather the use of conventional drugs such as temozolomide can enhance the MMR resistance and can also lead to further mutations leading to secondary malignancies.⁶ Surveillance is the means of diagnosing malignancy in patients with CMMRD, MRI brain is recommended on diagnosis and then every 6 months afterwards, colonic polyps are reported as early as 6 years of age so colonoscopy is recommended.⁷ Unfortunately no surveillance tool for haematological malignancy has been suggested.

Constitutional mismatch repair deficiency has emerged as a new entity, its diagnosis and management are challenging for oncologists. Early diagnosis of CMMRD is crucial especially in country like ours where consanguineous marriages are common. Early diagnosis will help in surveillance, identifying family members at risk and suggesting appropriate chemotherapy protocols.

CONCLUSION

Constitutional mismatch repair deficiency is a condition with variable clinical presentation, mimicking other hereditary syndromes, hence making the diagnosis difficult. Our case highlights the occurrence of cancer predisposition conditions among Pakistani population. With limited resources and lack of targeted therapies we can aim for sibling screening and genetic counselling in our country where consanguineous marriage is a part of culture.

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