BRIEF REPORT

Constitutional Mismatch Repair Deficiency Presenting in Childhood as Three Simultaneous Malignancies

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A 13-year-old child presented with three simultaneous malignancies: glioblastoma multiforme, Burkitt lymphoma, and colonic adenocarcinoma. She was treated for her diseases without success and died 8 months after presentation. Genetic analysis revealed a homozygous mutation in the PMS2 gene, consistent with constitutional mismatch repair deficiency. Her siblings and parents were screened; three of four siblings and both parents were heterozygous for this mutation; the fourth sibling did not have the mutation. Pediatr Blood Cancer 2013;60:E135–E136. © 2013 Wiley Periodicals, Inc.

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Constitutional mismatch repair deficiency (CMMRD) is a rare cancer predisposition syndrome related to Lynch syndrome. CMMRD is known for the clinical findings of colorectal polyposis, brain tumors, hematological malignancies and phenotypic features suggestive of neurofibromatosis type 1 (NF1) [1]. We report a case of CMMRD in a 13-year-old girl presenting with colonic polyposis, rectal adenocarcinoma, glioblastoma multiforme (GBM), and non-Hodgkin lymphoma.

CASE REPORT

A 13-year-old previously healthy, Mennonite female presented with bloody diarrhea, headaches, and vomiting. She had a 6-month history of crampy abdominal pain, intermittent bloody diarrhea, and a 5.5-kg weight loss. She had headaches and vomiting immediately prior to presentation. Physical examination revealed large areas of pigmented dysplasia over the right neck, shoulder, and arm, right forearm, and left upper chest. These lesions were reminiscent of café au lait spots but were more irregular than typical café au lait spots. There was no auxiliary freckling and no Lisch nodules on ophthalmologic exam. Examination of the abdomen revealed mild epigastric tenderness. The neurologic exam was normal. Past medical history was notable for congenital absence of several secondary teeth, and mild idiopathic thoracolumbar scoliosis. Family history was remarkable for a maternal great uncle who died of leukemia at age 12, maternal great aunt with cleft palate, and maternal great grandmother with colon cancer. There was no family history of NF1. A blood count revealed microcytic anemia with hemoglobin of 11.4 g/dL and a mean cell volume of 69.1 fl. A brain MRI obtained for worsening headaches revealed a 3.2-cm mass in the left frontal lobe. Chest CT and MRI of the cervical, thoracic, and lumbar spine were normal. MRI of the pelvis showed a 5-cm heterogeneous, lobulated, partially enhancing right adnexal mass. PET scan showed an additional, previously unsuspected lesion consistent with a rectal neoplasm.

The brain tumor was totally resected and found to be a GBM. Diagnostic laparoscopy was performed for evaluation of the pelvic mass which was found to be a Burkitt lymphoma. Colonscopy revealed multiple pedunculated and sessile polyps throughout the colon and rectum. A total colectomy with ileostomy was completed. The rectal polyps were adenocarcinoma. A total proctectomy was performed.

The decisions regarding therapy were complicated by the presence of three simultaneous neoplasms. Therapies directed against the GBM and Burkitt lymphoma were started simultaneously with 60 Gy of external beam radiation therapy to the brain and drugs active against the Burkitt lymphoma including vincristine, rituximab, and cyclophosphamide. Temozolomide was not given. Within 2 months of starting chemotherapy, her abdominal Burkitt lymphoma progressed. The chemotherapy regimen was then changed to cyclophosphamide, vincristine, methotrexate, rituximab, doxorubicin, and prednisone. Following completion of brain radiation therapy, her glioblastoma recurred. No specific therapy was given against the adenocarcinommas. She rapidly deteriorated and was discharged to home on hospice care. She died at home 8 months after initial presentation.

This highly unusual case prompted a discussion with surviving family members and the medical team regarding evaluations for cancer predisposition syndromes. The presentation was highly suggestive of mismatch repair (MMR) deficiency syndrome so further testing on surviving family members was recommended. The surviving four siblings (ages 7, 12, 15, and 17) and parents (both 40 years of age) consented to genetics consultations and colonoscopies. The family denied history of childhood cancers or Lynch type neoplasms in close relatives. Colonoscopies revealed one sibling with a few benign polyps; the other three sibs had normal colonoscopies. Both parents had normal colonoscopies. Parents agreed to molecular testing of the proband. Sequencing and deletion/duplication testing was negative for MSH2, MLH1, and...

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**MSH6.** Since the clinical picture was so suggestive of CMMRD, PMS2 testing was then completed. We identified a homozygous PMS2 missense mutation c.2095G>C; p.Asp699His). Subsequent testing confirmed that both parents and three of the four siblings (including the one with benign polyposis) were heterozygous for this mutation; the fourth sibling did not have the mutation. The affected siblings and both parents were referred to our hereditary cancer syndrome clinic for appropriate screening and long-term follow-up.

**DISCUSSION**

CMMRD is a rare cancer predisposition syndrome related to Lynch syndrome. CMMRD is known for the clinical findings of early onset colorectal polyposis, primary brain tumors, hematologic malignancies and phenotypic features suggestive of neurofibromatosis type 1, specifically hyperpigmented lesions resembling *café au lait* spots [2,3]. Heterozygous mutations in the MMR genes (MLH1, MSH2, MSH6, or PMS2) cause Lynch syndrome (hereditary non-polyposis colorectal cancer), inherited in an autosomal dominant fashion. Biallelic, germline mutations in these genes lead to the more severe cancer predisposition syndrome CMMRD [1,4-6]. The majority of patients with CMMRD have mutations of PMS2 (as in this case) or MSH6 [4,7,8]. Patients with CMMRD due to mutations in PMS2/MSH6 are more likely to have more than one malignancy compared to patients with mutations in *MLH1/MSH2* [1].

Since CMMRD is caused by the mutations in the same genes as Lynch syndrome, and Lynch syndrome follows an autosomal dominant inheritance pattern, one would expect to see Lynch syndrome-associated cancers in family members. However, the two MMR genes implicated most frequently in CMMRD (MSH6 and PMS2) have been shown to have lower penetrance than MLH1 and MSH2 mutations and are associated with later presentation of associated cancers. Thus, children presenting with malignancies associated with CMMRD may not have a family history of Lynch-associated cancers, as was the case with this patient, but should still be evaluated for MMR gene mutations [4,9].

The three most common cancer types seen in patients with CMMRD (and the most common cancer subtype in each group) include hematologic malignancies (non-Hodgkin lymphoma), brain tumors (GBM), and Lynch syndrome-associated tumors (colorectal cancer). Our patient presented with each of these three neoplasms. More than two-thirds of patients with CMMRD have *cafe au lait* like lesions, as did our patient [1].

The brain tumor seen in this case was GBM, an aggressive, malignant glioma with a poor prognosis. The use of temozolomide chemotherapy has helped to improve outcomes in adults with GBM [10]. However, temozolomide was not given to this patient because tumors in individuals with constitutional defects in MMR can be resistant to methylating agents, such as temozolomide. Typically, in mutated cells, when O2'-methylated guanine nucleotides incorrectly pair with thymine during DNA replication, the MMR system is activated, leading to futile cycles of repair that culminate in apoptosis of the malignant cells [11]. Patients with MMR defects fail to halt DNA replication under these conditions and the cancerous cells are able to continue to multiply in the presence of temozolomide. Methylating drugs like temozolomide may not only be ineffective, they may be especially toxic to MMR-deficient patients [4].

In summary, we present a child with three simultaneous malignancies, and the distinctive physical findings, highly suggestive of CMMRD. Molecular testing revealed biallelic PMS2 mutations, confirming the diagnosis of CMMRD. The diagnosis of CMMRD in a child with cancer may be difficult. According to Wimmer, CMMRD-D should be considered in the differential diagnosis in all patients with malignancies, except clearly NF-1-associated tumors, who have one or more of the following: *cafe au lait* macules or other signs of NF1, consanguineous parents, a family history of Lynch syndrome-associated tumors, a second malignancy or a sibling with childhood cancer [1].

**REFERENCES**