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Simultaneous Colonic Adenocarcinoma and Medulloblastoma in a 12 year old with Biallelic Deletions in *PMS2*

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Abstract

We describe a 12 year old simultaneously presenting with colonic adenocarcinoma and medulloblastoma from biallelic deletions in the mismatch repair gene *PMS2*. Her distinctive physical and clinical findings are characteristic of constitutional mismatch repair deficiency syndrome. Earlier recognition of such findings may permit better screening and more effective treatment.

Keywords

Constitutional Mismatch Repair Deficiency; Lynch Syndrome; HNPCC

Case Presentation

The patient presented at age 11 with abdominal pain, bloody diarrhea, and a history of multiple pneumonias and otitis media. Esophagogastroduodenoscopy and colonoscopy were negative. She was diagnosed with systemic lupus on the basis of pancytopenia, proteinuria, along with high titer ANA, anti-double stranded DNA, and anti-smooth muscle antibodies. Treatment was begun on hydroxychloroquine and prednisone. Based on CT, she was also diagnosed with bronchiectasis of uncertain etiology. Physical exam was notable for several hypopigmented areas and overall mottled pigmentation.

After further incidents of rectal bleeding, she presented 10 months later at age 12 with intussusception, reduced by contrast enema. Colonoscopy revealed two sizable colonic polyps in an otherwise normal colon (Figure 1A). Pathology showed both to be tubulovillous adenomas, one with a central area of adenocarcinoma penetrating the bowel wall into surrounding lymphatic tissue. Staging workup revealed four hypodense areas in the liver consistent with metastatic adenocarcinoma (Figure 1B).

Though her neurologic exam was normal, MRI of the brain was performed and revealed a cerebellar tumor (Figure 1C). The tumor was completely resected and found to be a classical medulloblastoma (Figure 1D) with no evidence of dissemination. Subsequently, she had a

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Note: All gene names conform to HUGO nomenclature: <http://www.genenames.org>

left hemicolectomy along with an excisional biopsy confirming two of the liver metastases. Remarkably, she had no significant family history of malignancy.

The patient received 7 cycles of FOLFOX chemotherapy for her adenocarcinoma with concurrent craniospinal radiation therapy for the medulloblastoma (2340 cGy whole brain and spine with 3240 cGy to the tumor bed). After 3 cycles of Irinotecan, 5-Fluorouracil, and Leukovorin, follow up MRI showed no recurrence of her medulloblastoma and improvement in her hepatic metastases. Residual hepatic disease was subsequently resected, rendering her disease free from both tumors.

However, nine months from diagnosis, the patient was admitted for sudden onset dizziness, bitemporal headache, slurred speech, and ataxia. MRI was consistent with leukoencephalopathy and necrosis in the pons, middle cerebellar peduncles, and midbrain. No infectious causes were found. Further chemotherapy was discontinued and treatment of her leukoencephalopathy with Dexamethasone and IVIG was instituted with mixed effects. Twenty-three months from diagnosis, new hepatic lesions were noted and were biopsy confirmed as adenocarcinoma. The family declined further therapy and these lesions remained radiographically stable until her demise from pulmonary compromise and progressive leukoencephalopathy forty months from diagnosis.

Genetic studies at diagnosis was a negative for FAP. Microsatellite instability testing on her tumor was positive in 5 of 5 markers tested, consistent with hereditary nonpolyposis colon cancer (HNPCC)/Lynch syndrome. Subsequent testing by immunohistochemistry showed normal expression of MLH1 and MSH2 protein, but no detectable MSH6 or PMS2. Bi-directional sequencing and multiplex ligation-dependent probe amplification (MLPA) testing revealed no coding mutations or deletions/duplications of *MSH6*. However, subsequent MLPA testing revealed large biallelic *PMS2* deletions (exons 7–11 and exons 7–14) consistent with constitutional mismatch repair deficiency (CMMR-D). Further genetic testing was declined by the family.

Discussion

The occurrence of brain tumors and colon carcinoma in a single patient is clinically designated as Turcot syndrome¹, also known as brain tumor polyposis syndrome^{2, 3}. Of two classical subtypes, Type 1 Turcot is a subset of Lynch Syndrome/HNPCC⁴ and is associated with heterozygous germ line inactivating mutations in one of the four mismatch repair genes (MMR)—*MSH2*, *MLH1*, *MSH6*, and *PMS2*. Inheritance is autosomal dominant and patients present in early adulthood. Type 2 Turcot involves germline inactivating mutations in the *APC* gene, also an autosomal dominant trait of high (80%) penetrance⁵. Individuals present with colonic polyposis as in familial adenomatous polyposis (FAP), brain tumors developing in the adult years.

Our patient did not fit well into either category due to the very young age of presentation, the lack of associated features such as polyposis or a positive family history, and the additional un-explained features such as her Lupus and skin findings. However, these clinical features are consistent with biallelic germline mutations in MMR genes known as Constitutional Mismatch Repair Deficiency (CMMR-D) syndrome^{6, 7}. Although Lynch syndrome has dominant inheritance, the mode of inheritance for CMMR-D is recessive. The reduced penetrance of *PMS2*-associated Lynch syndrome likely explains the negative family history. Crucially, the two hits present at birth foreshorten the course of the disease and brain tumors, colon cancer, and other malignancies⁸ have been reported to occur in childhood and adolescence. So, even before genetic testing was performed, we believed our patient had CMMR-D.

Several initially unexplained aspects of this patient's complex presentation clearly fall within the CMMR-D clinical spectrum. Since CMMR-D patients frequently exhibit café au lait macules and may show other manifestations typical of Neurofibromatosis Type 1 including axillary freckling and Lisch nodules⁹, her skin findings entirely consistent. Also notable are prior reports of Lupus in CMMR-D patients with *MSH6* mutations^{10, 11}. Our patient demonstrates that *PMS2* biallelic mutations can also be associated with Lupus.

Other remarkable aspects of this patient's course are not yet recognized as part of the CMMR-D spectrum. Since there is no published evidence of FOLFOX chemotherapy being associated with radiosensitization, our patient's constitution may have contributed to the severe and unexpected CNS toxicity. No association between CMMR-D and radiosensitivity has been previously reported. Similarly, her persistent bronchiectasis has not been described before in association with CMMR-D.

Our report is the only known case of simultaneous occurrence of colon cancer and medulloblastoma. In addition, this is the only known report of large bi-allelic deletions within the *PMS2* gene. All *PMS2*-associated CMMR-D reports to date have been described in patients with two point mutations/small indels or a point mutation/small indel and one large deletion. CMMR-D is an emerging disease entity that predisposes to the early onset of multiple cancers. The key to better care for such patients is an early recognition of the distinctive physical and clinical findings which patients exhibit even before they present with malignancy, so that early screening may be instituted. We hope this report will lead to an increased awareness of this constellation of findings on the part of pediatric practitioners.

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Abbreviations

cGy	Centigray
CMMR-D	Constitutional Mismatch Repair Deficiency
FAP	Familial Adenomatous Polyposis
FOLFOX	Folinic Acid, Fluorouracil, Oxaliplatin
HNPCC	Hereditary Non-Polyposis Colon Cancer
MMR	Mismatch Repair
MPLA	multiplex ligation-dependent probe amplification

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Figure 1.

A: A polyp found on endoscopy after reduction of intussusception. B: Histology of the adenocarcinoma (H&E section of a liver metastasis). C: MRI showing the posterior fossa tumor. D: Brain tumor histology consistent with Classical Medulloblastoma (H&E section). The tumor stained positively for Vimentin, GFAP, PGP 9.5, and Synaptophysin.