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Metachronous T-lymphoblastic lymphoma and Burkitt lymphoma in a child with constitutional mismatch repair deficiency syndrome

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Abstract

Constitutional mismatch repair deficiency (CMMRD) is a cancer predisposition syndrome associated with a high risk of developing early-onset malignancies of the blood, brain and intestinal tract. We present the case of a patient with T-lymphoblastic lymphoma at age three, followed by Burkitt lymphoma ten years later. This patient also exhibited numerous nonmalignant findings including café au lait spots, lipomas, bilateral renal nodules, a non-ossifying fibroma, multiple colonic adenomas, and a rapidly enlarging pilomatrixoma. The spectrum of malignant and nonmalignant neoplasms in this patient highlights the remarkable diversity, and early onset, of lesions seen in children with CMMRD.

Keywords

lymphoma; oncology; predisposition; hereditary

Introduction

Constitutional mismatch repair deficiency (CMMRD) is a cancer predisposition syndrome typified by early onset malignancies of the central nervous, gastrointestinal, and hematologic systems. CMMRD is caused by bi-allelic mutations in genes that regulate DNA mismatch repair, including *MLH1*, *MSH2*, *MSH6* and *PMS2*. Hematologic malignancies observed in CMMRD are predominately T-cell lymphoblastic lymphoma (T-LL), and less commonly, acute leukemia.[1–4] Here, we present an unusual case of a patient with CMMRD who developed early onset T-LL, followed ten years later by a mature B-cell lymphoma. This

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patient also exhibited café au lait macules (CALM) and numerous other neoplasms. While nonmalignant manifestations of CMMRD such as adenomatous polyps and neurofibromas have been described, the extensive nonmalignant abnormalities observed in our patient highlight the diversity of findings in this condition.

Case Description

A 3 year-old male initially presented with T-LL. The T-LL had a normal karyotype and was successfully treated based on NHL-BFM-90 with intrathecal chemotherapy instead of cranial irradiation. He went into remission and completed therapy at the age of 5 years. He re-presented at age 13 with abdominal pain and was found to have an ileal mass. The mass and multiple incidentally identified colonic polyps were biopsied via colonoscopy, at which time pathology revealed Burkitt lymphoma and colonic tubular adenomas (Figure 1A and 1B). Staging revealed bony metastatic disease without bone marrow involvement. Multiple CALM were noted on physical exam. His Burkitt lymphoma was treated using LMB-96 backbone therapy without alteration apart from addition of dexrazoxane prior to doxorubicin. He achieved remission and did not experience significant treatment complications.

Because of the history of metachronous malignancies, CALM, and multiple colonic polyps, he was evaluated for an underlying cancer predisposition syndrome. Family history revealed colon polyps in his maternal grandmother; two of her sisters (our patient's great aunts) died from kidney and esophageal cancer, respectively. His maternal grandfather died from melanoma. The maternal family history did not meet Amsterdam II criteria for Lynch syndrome.[5] The paternal family history was largely unknown. The patient's colon polyps were evaluated for mismatch repair protein expression via immunohistochemistry (IHC), which revealed lack of PMS2 in polyps and surrounding normal tissues (Figure 1C and 1D). To confirm IHC findings, *PMS2* gene sequencing was performed and revealed biallelic pathogenic mutations, c.736_741del6ins11 and c.1831dupA. Both mutations result in frameshift changes leading to premature termination. Further testing of the patient's mother revealed that she carried the c.1831dupA *PMS2* mutation. The father has not been tested.

In the context of his CMMRD diagnosis and colonic polyps, serial surveillance with esophagoduodenoscopy, colonoscopy, and capsule endoscopy was initiated. Prior to his first surveillance colonoscopy, a PET scan performed for Burkitt lymphoma disease evaluation 4 months after the start of therapy revealed a highly PET avid mass in his sigmoid colon. Subsequent colonoscopy revealed a 2×5 cm sigmoid polyp with focal high-grade dysplasia and 12 smaller polyps without dysplasia. All visualized polyps were removed. Colonoscopies performed 2 and 4 months later showed interval development of 8-10 new polyps. Because of the rapid recurrence of polyps, the patient opted for prophylactic total proctocolectomy. Currently, he is cancer free, twenty months from diagnosis of Burkitt lymphoma and seven months from proctocolectomy.

In addition to his 2 hematopoietic malignancies, the patient's history is remarkable for a lipoma surgically resected at age 3, a pituitary cyst diagnosed at age 10, a tibial non-ossifying fibroma diagnosed at age 11, stable bilateral renal lesions of unknown etiology

diagnosed at age 13, and a rapidly growing pilomatrixoma surgically resected at age 14 (Figure 2). He will undergo serial surveillance predicated upon recent guidelines.[6·7]

Discussion

The DNA mismatch repair system, comprised of 4 proteins encoded by the genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, is critical for protection against oncogenesis. Mono-allelic germline mutations cause Lynch syndrome and lead to increased risk of gastrointestinal, endometrial and other malignancies, primarily occurring in adults. In comparison, CMMRD is an autosomal recessive syndrome resulting from mutational inactivation of both alleles of a mismatch repair (MMR) gene. Due to complete loss of MMR function, patients with CMMRD are at increased risk to develop malignancies involving the central nervous, gastrointestinal and hematologic systems, with onset in childhood. Patients frequently manifest with CALM that resemble lesions seen in neurofibromatosis type 1.[8] In CMMRD, *PMS2* is the most commonly mutated gene, followed by *MSH6*[1] In contrast, the most commonly affected genes in Lynch syndrome are *MLH1* and *MSH2*, with mono-allelic *PMS2* and *MSH6* mutations resulting in reduced penetrance.[9] This reduced penetrance explains why family history may not be suggestive for Lynch syndrome in patients with CMMRD.

CMMRD stands in contrast to other conditions that predispose to hematological malignancies. First, lymphoma predisposition most commonly occurs in the context of inherited and acquired immunodeficiencies.[10] While altered immunoglobulin class switch recombination has been reported, patients with CMMRD do not typically exhibit clinical immunodeficiency.[11] Second, most known germline variants that predispose to acute lymphoblastic leukemia (ALL) preferentially increase the likelihood of B-ALL rather than T-ALL.[12] The most common hematologic malignancy seen in CMMRD is T-LL rather than B-LL.[4] Mature lymphoid neoplasms have been reported rarely.[1·3·8·13·14] Curiously, all patients with CMMRD associated mature B-cell lymphoma reported to date harbor bi-allelic *PMS2* mutations.[3·8·13·14] In two cases, mature B-cell lymphoma was the initial malignancy diagnosed, excluding the possibility that they were treatment related. In other cases, the relative pathogenic contributions from prior chemotherapy versus germline tumor predisposition cannot be determined.

Non-malignant abnormalities also may occur in CMMRD syndrome. CALM macules are found in the majority of patients with CMMRD. Agenesis of the corpus callosum occurs in a minority (3-6%) of patients.[13] Other brain malformations such as cavernomas and angiomas have also been reported.[3] Reported premalignant conditions or non-malignant tumors include intestinal polyps, hepatic adenomas, neurofibromas, optic gliomas, and pilomatrixomas.[1] Our patient experienced multiple non-malignant manifestations, emphasizing the broad array of abnormal growths that can occur in children with CMMRD.

The rationale and a schedule for surveillance of patients with CMMRD have recently been proposed.[6·7] While the efficacy of these protocols remains an area of active investigation, there is early evidence that surveillance can identify small solid and central nervous system tumors (such as early stage colorectal carcinomas and low grade gliomas) that are amenable

to complete surgical resection in a limited number of CMMRD patients.[6-8] It remains to be determined whether surveillance will be of benefit in the detection and treatment of hematopoietic malignancies.

This case represents an unusual presentation of a patient with CMMRD who developed T-LL followed by mature B-cell neoplasm. This case supplements the limited existing literature through illustration of multiple important points. First, while the vast majority of hematological malignancies in CMMRD are T-LL, mature B-cell lymphomas can rarely occur. Second, a long lag time between cancer diagnoses may occur, as exemplified by the ten year interval between neoplasm diagnoses in our patient. Third, in contrast to other syndromes associated with increased DNA damage (e.g., Fanconi anemia), patients with CMMRD do not appear to experience excessive toxicity from chemotherapy and therefore reduced intensity approaches to cancer treatment are not indicated at this time.[3] Fourth and finally, patients presenting with a second neoplasm, or the combination of CALM and a malignancy, should prompt consideration of CMMRD guided by recently proposed diagnostic criteria.[1]

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Abbreviations key

CMMRD	constitutional mismatch repair deficiency
T-LL	T lymphoblastic lymphoma
CALM	café au lait macules
IHC	immunohistochemistry

Figure 1.

Representative photomicrographs of colonic polyps. **A:** (20× magnification) Hematoxylin and eosin stained sections of polyps showed tubular adenoma, **B:** (400× magnification) with characteristic pseudostratified dysplastic nuclei, **C and D:** (400× magnification) Paraffin immunohistochemistry for MLH1 (**C**) and PMS2 (**D**) showed loss of expression of the latter. Retained expression similar to MLH1 was seen for MSH2 and MSH6.

Figure 2.

Examples of tumors identified in our patient. **A:** Colonoscopy image of a large sigmoid polyp shown to have high grade dysplasia **B:** Axial CT image from positron emission tomography-CT shows a sharply circumscribed, cortically based, left femoral, benign fibrocortical defect. **C:** Axial contrast-enhanced computed tomography (CT) image showing right renal lesion (arrow) **D:** Sagittal 3D MPRAGE (magnetization prepared rapid acquisition gradient recalled echo) MR image showing pituitary lesion (straight arrow) with cystic component (curved arrow).