Colorectal Cancer due to Constitutional Mismatch Repair Deficiency Mimicking Neurofibromatosis I

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Colorectal carcinoma (CRC) is an extremely rare tumor of childhood that can be associated with cancer predisposition syndromes. A patient with CRC related to constitutional mismatch repair deficiency (CMMRD) syndrome with features of neurofibromatosis type 1 (NF-1) is presented here. A 13-year-old boy was admitted for a 4-month history of diarrhea and rectal bleeding. The patient had extensive café au lait spots, freckling, and Lisch nodules. He fulfilled the NF-1 diagnostic criteria. Colonoscopy showed numerous polyps and a colorectal mass lesion, of which a biopsy revealed adenocarcinoma, an uncommon pathology associated with NF-1. High microsatellite instability and homozygous mutation of *PMS2* gene in tumor tissue and blood lymphocytes, respectively, confirmed the diagnosis of CMMRD. Unfortunately, because family history related to CMMRD was negative, the parents denied the diagnosis and refused the therapy, and the patient was lost to follow-up. CMMRD is a rare cancer predisposition syndrome with phenotypical features resembling NF-1. The disease may be suspected in the setting of NF-1 features and CRC, high-grade brain tumors, or hematologic malignancies. Lack of family history related to CMMRD may be a major obstacle to convincing parents of the presence of an inherited disease in their progeny.

The DNA mismatch repair (MMR) system is a key pathway contributing to maintenance of genomic stability. The system recognizes, removes, and restores base substitution and insertion–deletion mismatches during DNA replication.[1] In case of MMR deficiency, erroneously inserted nucleotides give rise to high microsatellite instability, which may result in a distinct spectrum of cancers.

MLH1, MSH6, MSH2, and *PMS2* genes are involved in the mismatch repair system. Heterozygous mutations of these genes cause the autosomal dominant Lynch syndrome (LS), which predisposes typically to colorectal cancer (CRC), usually after the fourth decade of life. Biallelic mutations of MMR genes cause a distinct autosomal recessively inherited cancer predisposition, namely constitutional mismatch repair deficiency (CMMRD) syndrome.[2] The neoplastic spectrum of CMMRD includes hematologic malignancies, central nervous system tumors, and CRCs at an earlier age than expected. Since the first case reported in 1999, 146 cases of CMMRD from 91 families have been documented. Many patients with CMMRD have café au lait spots (CLS) and other features of neurofibromatosis type 1 (NF-1) such as freckling, neurofibromas, Lisch nodules, tibia pseudoarthrosis, sphenoid wing dysplasia, and optic glioma.[3] Lisch nodules are very rare (5 in 146), and the number of CLS does not always reach diagnostic criterion for NF-1 in majority of patients. Here we report the case of a patient with CMMRD and CRC, without familial

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history of LS-related cancer or CLS, who initially received a diagnosis of NF-1 based on clinical criteria including extensive CLS, Lisch nodules, and axillary freckling.

CASE

A 13-year-old boy presented with rectal bleeding and diarrhea of 4 months' duration. Personal history was unremarkable except poor school performance. His parents were first-degree cousins. No family history of cancer was described. Family members including his 32-year-old mother, 36-year-old father, and 8-year-old brother did not have CLS or freckling. The paternal grandmother and grandfather (65 and 79 years old, respectively) and 80-year-old maternal grandmother and maternal grandfather (who died in a traffic accident) did not have features of LS-related disease spectrum. Physical examination findings were as follows: weight 40 kg (10th–25th percentile), height 156 cm (50th percentile), right palpebral ptosis, and right esotropia, spontaneous nystagmus, >20 CLS ranging in size from 0.5 to 20 cm in diameter, axillary freckling, and pes planus at left foot. Hypopigmented lesions were negative. Dysmetria, dysdiadochokinesia, and ataxia were positive, and deep tendon reflexes were increased. Ophthalmologic examination was positive for Lisch nodules. Laboratory findings were within normal limits except mild iron deficiency anemia.

In brain MRI, T2 hyperintense, contrast nonenhanced focal areas of signal intensity (largest 1.5 cm) were identified in the right cerebellar hemisphere, vermis, pons, left to supratentorial midline areas, and bilaterally subependymal parietal areas in subcortical white matter. Hydrocephalus due to aqueductal stenosis was also present. There was no corpus callosum agenesia. Upper gastrointestinal endoscopy findings were within normal limits except mild nodular appearance in the duodenum. Colonoscopy showed multiple polypoid lesions in the terminal ileum and colon. Ten centimeters distal to the anal sphincter, an ulcerative cauliflower-like mass with partial obstruction of the rectosigmoid lumen was observed. The biopsies of rectal mass, polyp from the ascending colon, and healthy-appearing colon revealed adenocarcinoma, adenomatous polyp, and tubular adenoma, respectively. Staging evaluations revealed abdominal multiple lymphadenopathies without distant metastasis. The diagnoses were stage IIIA CRC associated with NF-1 according to National Institutes of Health Consensus Development Criteria. However, although NF-1 is a cancer predisposition syndrome, CRC is not clearly associated with NF-1. Thus, the differential diagnosis included other cancer predisposition syndromes presenting with CLS, including Fanconi anemia, Nijmegen breakage syndrome, Bloom syndrome, Noonan syndrome, and CMMRD. But clinical findings were not consistent with any of these syndromes except CMMRD. Colorectal tumor tissue was positive for high microsatellite instability, highly suggestive of a DNA MMR defect. Mutation analyses of the *NF1* gene and *MLH1, MSH2,* and *MSH6* genes were negative, but a homozygous mutation (c.1571dupC (p. Gly525Argfs*17)) was identified in the *PMS2* gene, confirming the diagnosis of CMMRD. Because no family members had cancer or skin findings, parents did not accept the diagnosis and refused therapy. The importance of surveillance studies including MRI scanning for brain tumors and screening for hematologic malignancies was reemphasized. Phone communication with the father revealed that the patient was brought to 3 medical centers for consultations, and the diagnosis of CRC was reconfirmed. Unfortunately, the family declined medical care and genetic counseling, and the patient was lost to follow-up.

DISCUSSION

DNA MMR machinery is an excellent and vital system that maintains the integrity of the human genome by repairing naturally occurring replication errors such as mispairs, insertions, or deletions. The system is controlled by MMR genes, of which biallelic germline mutations lead to CMMRD syndrome.[3] According to molecular analyses of 146 previously documented patients with CMMRD, ~58% of cases are caused by *PMS2* mutations, as our patient had. Twenty-two percent and 20% of cases are caused by *MLH1* or *MSH2* and *MSH6* mutations, respectively. A majority of patients with CMMRD show some features reminiscent of NF-1,[4] mainly CLS, but the presence of ≥6 CLS, a diagnostic requirement for NF-1, is not always present. According to the same report, Lisch nodules and freckling were reported in 5 and 14 out of 146 patients, respectively. Our patient had countless CLS, freckling, and Lisch nodules, and there was no doubt that the patient had NF-1 according to his phenotypical features on admission. However, neither our patient nor other patients with CMMRD tested so far had a pathogenic germline mutation for NF-1.[5]

Leukemia, lymphoma, brain tumors, glial tumors, rhabdomyosarcoma, neuroblastoma, and Wilms tumor are commonly reported in both NF-1 and CMMRD. Currently, it is known that the phenotype of NF-1 and CMMRD may be indistinguishable. NF-1 is diagnosed on the basis of clinical criteria. Routine molecular testing is not mandatory and is not readily available in every institution, including ours. Therefore, one may interpret the diagnosis as NF-1 on clinical grounds in the aforementioned tumors with NF-1–like features, and the diagnosis of CMMRD might be overlooked, with the consequence of inappropriate management in terms of counseling, treatment strategy, and prognosis.

In 2014, the European consortium Care for CMMRD (C4CMMRD)

suggested a scoring system for the suspected diagnosis of CMMRD.[4] Although the validity of the recommended indication criteria has not been tested, at <25 years of age, any carcinoma from the LS spectrum (colorectal, endometrial, small bowel, ureter, renal pelvis, biliary tract, stomach, and bladder carcinoma) or multiple bowel adenomas in the absence of *APC*/*MUTYH* mutations or a single high-grade dysplasia adenoma deserves to be investigated for CMMRD (Table 1).

CRC in association with CMMRD has been described in many studies. Cases accumulate around the ages of 12 to 17 years, and the frequency declines after the second decade. A majority of patients with CRC have >10 adenomas.[3] Patients may present with rectal bleeding at a late stage, as our patient did. Metastatic disease is present in ~50% of cases at the time of diagnosis.

Early identification of patients with CMMRD might have an influence on management of CRC cases. Previous studies of patients with LS-CRC reported better survival in comparison with non–LS-CRC cases. Because the number of CMMRD-CRC cases is limited, it is not possible to make such an assumption. In addition, antineoplastic sensitivity might be altered in CMMRD, a phenomenon previously described in LS-CRC cases treated with 5-fluorouracil alone.[6] Given the fact that many chemotherapy agents exert their action through DNA damage and require an intact MMR system, patients with CRC-CMMRD might not benefit from certain forms of chemotherapy.

Although it is not a must, a familial or personal history of LS-related cancer is expected in patients with CMMRD. However, the absence of LS-related cancer history or other documented physical findings of CMMRD among family members might lead to denial of diagnosis, with consequent distrust toward health professionals, as in our experience. The diagnosis of inherited cancer is a significant cause of emotional burden. A previously healthy family suddenly faces 2 diagnoses, namely cancer and CMMRD, the former of which might lead to loss of their affected child, the latter of which might negatively influence all family members. The parents are immediately expected to decide on cancer treatment and genetic counseling before they are able to process and absorb the impact of the situation, as happened in our case. Parents might feel guilt and shame, as if the consanguinity is the cause of disease in their child, a situation that might blur their decisions. Also, family members positive for CMMRD who do not develop cancer might experience anxiety and distress. As health professionals, we need to understand and address the psychosocial implications of genetic testing for CMMRD and other inherited cancer syndromes to avoid refusal of medical care.

CLS are common in healthy and cancerous children.[7] In patients presenting with CLS or NF-1–like features and cancer, the diagnostic criteria proposed by C4CMMRD might be beneficial for elucidating the distinction between CMMRD and NF-1. A high index of suspicion for CMMRD should be maintained in case of a clearly non–NF-1 associated malignancy (ie CRC) presenting with features of NF-1. Timely identification of CMMRD and appropriate surveillance protocols might increase the chances of survival for cancer. Affected patients should be regularly screened by clinical assessment, complete blood cell count, tumor markers, brain MRI, and gastrointestinal endoscopy. Parents and patients should be educated about the signs and symptoms that may represent certain types of cancer. Increased awareness and better understanding of CMMRD among health care providers for children can contribute to early diagnosis. The psychosocial impact of predictive genetic testing should not be overlooked in those families.

TABLE 1 Diagnostic Criteria for Constitutional Mismatch Repair Deficiency Syndrome: Suggestions of the European Consortium C4CMMRD

Indication for CMMRD Testing in a Patient With Cancer	≥3 Points
Malignancies and premalignancies: 1 is mandatory; if >1 is present in the patient, add the points	
Carcinoma from the LS spectrum[a] at age <25 y	3 points
Multiple bowel adenomas at age <25 y and absence of *APC*/*MUTYH* mutations or a single high-grade dysplasia adenoma at age <25 y	3 points
World Health Organization grade III or IV glioma at age <25 y	2 points
NHL of T-cell lineage or sPNET at age <18 y	2 points
Any malignancy at age <18 y	1 point
Additional features: Optional; if >1 of the following is present, add the points	
Clinical sign of NF-1 or ≥2 hyperpigmented or hypopigmented skin alterations >1 cm in the patient	2 points
Diagnosis of LS in a first-degree or second-degree relative	2 points
Carcinoma from LS spectrum[a] before the age of 60 in first-degree, second-degree, or third-degree relative	1 point
A sibling with carcinoma from the LS spectrum,[a] high-grade glioma, sPNET, or NHL	2 points
A sibling with any type of childhood malignancy	1 point
Multiple pilomatricomas in the patient	2 points
1 pilomatricoma in the patient	1 point
Agenesis of the corpus callosum or non–therapy-induced cavernoma in the patient	1 point
Consanguineous parents	1 point
Deficiency or reduced levels of immunoglobulin G 2/4 or immunoglobulin A	1 point

NHL, non-Hodgkin lymphoma; sPNET, supratentorial primitive neuroectodermal tumors.

[a] Colorectal, endometrial, small bowel, ureter, renal pelvis, biliary tract, stomach, bladder carcinoma.

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ABBREVIATIONS

C4CMMRD: Care for CMMRD
CLS: café au lait spots
CMMRD: constitutional mismatch repair deficiency
CRC: colorectal carcinoma
LS: Lynch syndrome
MMR: mismatch repair
NF-1: neurofibromatosis type 1

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