Biallelic Mismatch Repair Deficiency – a rare and trouble genetic syndrome

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Case Report

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Abstract

Biallelic Mismatch Repair Deficiency (BMMRD) is a rare autosomal recessive disorder characterized by numerous cancers presenting as early as the first decade of life. Biallelic germline mutations in one of four mismatch repair (MMR) genes (*MLH1, MSH2, MSH6,* or *PMS2*) cause this devastating disease. Given the rarity of the syndrome, often-asymptomatic tumors and overlap with neurofibromatosis-1, diagnosis is frequently unrecognized or delayed. A high degree of clinical awareness is needed to identify new cases. Immunohistochemical assessment of MMR protein expression and analysis of microsatellite instability are the first tools with which to initiate the study of this syndrome in solid malignancies. MMR immunohistochemical shows a hallmark pattern with absence of staining in both neoplastic and non-neoplastic cells for the biallelic mutated gene.

We present a unique case of a young boy diagnosed with invasive colon adenocarcinoma and brain tumor, with classical BMMRD features, found to have biallelic pathogenic PMS2 mutations.

Introduction

Biallelic Mismatch Repair Deficiency (BMMRD) is a rare autosomal recessive disorder, there being just over 200 reported patients with this entity in the entire world [1]. Patients with this disorder born with biallelic inactivation of any one of the mismatch repair (MMR) genes (most commonly *PMS2*) and consequently have no DNA MMR activity in any tissue. This is different to Lynch Syndrome (LS), the most common cause of hereditary adult-onset colorectal cancer, where patients have a heterozygous variant in one of the MMR genes [2–4].

Affected individuals have been described with childhood onset (as early as the first decade of life) of gastrointestinal tumors, brain tumors, hematologic, urological and gynecological malignancies. Gastrointestinal and brain tumors are the most common malignancies described in BMMRD. While up to two-thirds of patients present with colonic tumors, diagnosis is difficult, as they do not often present with painless rectal bleeding as seen with other pediatric polyposis syndromes [3, 5–7]. Notable defining features of this disease include café-au-lait macules (similar to neurofibromatosis-1), found in the majority of patients, and a family history of consanguinity, which has been described in approximately half the reported diagnoses [3, 4].

We present a unique case of a 18-year-old young male diagnosed with invasive colon adenocarcinoma and, later, with brain tumor, with classical BMMRD features, found to have biallelic pathogenic PMS2 mutations. This case provides insights on how to identify BMMRD and delivers consistent clinical care to individuals with this diagnosis.

Case Report

The patient is a 18-year-old boy who had been followed up in pediatrics since childhood for mitochondrial cytopathy (partial complex IV deficit), NAFLD, frontal cavernous angioma and tibial osteochondroma. He

had several café-au-lait macules since childhood, but the genetic study for neurofibromatosis type 1 was negative. As a relevant family history, he had healthy consanguineous parents (1st degree cousins) and his maternal grandfather had rectal cancer at age 50 (MSH2 and MLH1 study without pathogenic variants in 1988).

At age 15, the patient underwent a colonoscopy due to abdominal pain and increased bowel movements (including nocturnal stools). It revealed a 20mm polyp of the sigmoid that was completely removed (tubular adenoma with low-grade dysplasia) and a 40mm neoformation in the hepatic angle, whose biopsies revealed a well-differentiated adenocarcinoma. A laparoscopic right hemicolectomy was performed. The patient underwent adjuvant chemotherapy with FOLFOX6 (Oxaliplatin, Leucovorin, and 5-FU) once the staging was pT3 N2a (5/54) cM0 R0.

Due to early colon carcinoma, café-au-lait macules, parental consanguinity and family history of colorectal cancer, the patient was referred for genetic consultation due to the clinical suspicion of BMMRD syndrome. A genetic study of the surgical specimen was performed and revealed neoplasia and normal tissue with loss of PMS2 expression, without alteration in the expression of MLH1, MSH2 and MSH6. Then, the search for germline mutations of the MLH1/MSH2/MSH6/PMS2 genes was performed and the genetic study confirmed BMMRD, carrying a pathogenic germline variant in the PMS2 gene in homozygosity.

Our patient started periodic close surveillance, as did his parents who were diagnosed with LS. During follow-up of cavernous angioma, when the patient was 17 years old, an IDH-wildtype multiform glioblastoma (WHO grade IV) was identified on a brain MRI. The patient underwent neoadjuvant chemotherapy and radiotherapy. Subsequently, surgery was performed and is currently under nivolumab.

Discussion

Although colorectal cancer in children is rare, this case demonstrates that advanced disease can be diagnosed in the pediatric population. In these cases, the suspicion of genetic syndromes is important. In our patient, the presence of some typical features such as parental consanguinity and the presence of café-au-lait macules triggered further investigation into genetic diseases.

It is extremely important to recognize BMMRD given its association with additional cancers including small-bowel cancer, central nervous system tumors, hematologic malignancies and, rarely, urinary tract tumors. The European consortium “Care 4 CMMRD” published guidelines for diagnosis of BMMRD in 2014 [8], based on the knowledge of the disease from just 146 known patients. In 2017, US Multi-Society Task Force on Colorectal Cancer [3] expanded upon these guidelines with further diagnostic and surveillance recommendations for this vulnerable population.

Biallelic mutations have been reported in all four DNA MMR genes (*MLH1, MSH2*, *MSH6*, and *PMS2*). However, the majority of BMMRD patients with gastrointestinal (GI) cancers report biallelic mutations in *PMS2*. In classic LS, monoallelic carriers of *PMS2* variants have a lower penetrance for GI cancers. The

combination of the early-onset cancer in the proband, later-onset cancer in the parents, and incomplete penetrance for *PMS2*-LS leads to a family history that is often negative. This may also explain how two unrelated healthy individuals with heterozygote *PMS2* variants would remain unaffected and produced offspring without being aware of his/her own risk of cancer development [3].

In our case, once the diagnosis of BMMRD was established, close surveillance of the young boy and his parents was instituted. This allowed the early diagnosis and management of a new tumor in our patient.

It is important to be familiar with and know how to identify the genetic cause in patients and their family members as it provides information pertinent to lifelong medical screening. It is paramount for clinicians to always recognize the potential for a rare disease diagnosis both to provide the best care for our patients and to expand the knowledge and recognition of disorders such as BMMRD.

Declarations

Statements of ethics

The subject (currently 18 years old) gave his written informed consent to the submission of the case report to the journal.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.R. collected the data, wrote the manuscript, and is the guarantor of the article. C.B., C.S. and M.D.-R. revised and approved the final version.

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