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SPECIAL ARTICLE

Recommendations on surveillance and management of biallelic mismatch repair deficiency (BMMRD) syndrome: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer

Carol Durno,[1] C. Richard Boland,[2] Shlomi Cohen,[3] Jason A. Dominitz,[4,5] Frank M. Giardiello,[6] David A. Johnson,[7] Tonya Kaltenbach,[8] T. R. Levin,[9] David Lieberman,[10] Douglas J. Robertson,[11,12] Douglas K. Rex[13]

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The US Multi-Society Task Force on Colorectal Cancer, with invited experts, developed a consensus statement and recommendations to assist health care providers with appropriate management of patients with biallelic mismatch repair deficiency (BMMRD) syndrome, also called constitutional mismatch repair deficiency syndrome. This position paper outlines what is known about BMMRD, the unique genetic and clinical aspects of the disease, and reviews the current management approaches to this disorder. This article represents a starting point from which diagnostic and management decisions can undergo rigorous testing for efficacy. There is a lack of strong evidence and a requirement for further research. Nevertheless, providers need direction on how to recognize and care for BMMRD patients today. In addition to identifying areas of research, this article provides guidance for surveillance and management. The major challenge is that BMMRD is rare, limiting the ability to accumulate unbiased data and develop controlled prospective trials. The formation of effective international consortia that collaborate and share data is proposed to accelerate our understanding of this disease.

The US Multi-Society Task Force on Colorectal Cancer has produced a series of consensus statements, guidelines, and recommendations on topics related to the diagnosis and management of colorectal cancer (CRC).[1] Traditionally, the guidelines use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to evaluate the strength of evidence in the development of guidelines and recommendations.[2] Prior guidelines addressed issues such as the optimal approaches to screening for CRC, management of patients with adenomatous polyps of the colon, guidelines for the performance of colonoscopy, and the optimal approach to bowel preparation for colonoscopy.[3,4] In each instance, prospective controlled clinical trials were considered the gold standard for high-quality evidence.

Recently, the Task Force published guidelines for the evaluation and management of Lynch syndrome (LS), some of which were drawn from high-quality evidence, but others were developed from expert opinions because of the absence of optimal prospective clinical trials.[1] The strength of evidence is based on the science at any point in time, but clinical decisions must be made at all times in the context of the available studies. High-quality studies and evidence require the availability of a large number of research subjects.

METHODS

A computer-aided search of MEDLINE from 1999 to March 2016 was performed focusing on biallelic mismatch repair deficiency (BMMRD) syndrome and constitutional mismatch repair deficiency (CMMRD) syndrome. The search was restricted to English language articles. In addition, a search was conducted using references from accessed articles. Publications were retrieved, and the authors synthesized and assessed the available data. There were no controlled trials in BMMRD. Experts pooled their collective experiences to develop consensus guidelines as an initial attempt to produce more uniform approaches to patient management, and prioritize areas in greatest need of research. The Multi-Society Task Force is composed of gastroenterology specialists with a special interest in CRC, representing the following major gastroenterology professional organizations: American College of

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Gastroenterology, the American Gastroenterological Association Institute, and the American Society for Gastrointestinal Endoscopy. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition, and representatives of the Collaborative Group of the Americas on Inherited Colorectal Cancer also reviewed this article. This document was approved by the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition.

BMMRD CHARACTERISTICS

LS is the autosomal-dominant disease caused by a monoallelic germline mutation in a DNA mismatch repair (MMR) or *EPCAM* gene, and is the most common cause of inherited CRC.[5] LS is caused by a large number of heterozygous germline mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*, and the tumor DNA is characterized by microsatellite instability (microsatellite instability–high [MSI-H], or, by convention, MSI). Penetrance for cancer is incomplete in LS; the cumulative lifetime risk of CRC is variable depending on the gene mutated and sex, and ranges from 40% to 70% for women and men, respectively, for the genes *MSH2*, *MLH1*, and *MSH6*.[5] Penetrance for CRC is reduced substantially for LS associated with mutations in *PMS2*, ranging from 10% to 20%.[6-8] Patients with LS also are predisposed to extracolonic malignancies, primarily endometrial cancer (40% in women with mutations in *MSH2* and *MLH1*), and, to a lesser extent, other gastrointestinal and genitourinary cancers. These syndromes can be managed adequately by annual colonoscopy and appropriate gynecologic surgery.[1]

A rare and far more virulent cancer syndrome occurs in the setting of biallelic MMR gene mutations (biallelic MMR deficiency [BMMRD]) (OMIM database accession no. 2763000). This disorder also is called *constitutional MMR deficiency* (CMMRD), because those born with biallelic inactivation of any one of the MMR genes have no DNA MMR activity in any tissue. In contrast, in LS, gene expression from the one wild-type allele is sufficient for adequate DNA MMR activity until a second hit inactivates the wild-type allele from the unaffected parent. The consequent tumor tissue is DNA-MMR deficient, which permits MSI to ensue.

BMMRD is characterized by the absence of DNA-MMR activity from birth, and results in brain tumors, colonic polyposis, colorectal and small-bowel cancers, leukemias, and lymphomas (Table 1). Patients often have café-au-lait macules and other stigmata that can be mistaken for neurofibromatosis type 1.[9,10] Somatic mutations in the *NF1* gene as a consequence of constitutional absence of MMR activity are the presumed explanation for this occurrence.[11]

The lifetime risk of gastrointestinal cancer among BMMRD patients is the highest reported of all gastrointestinal cancer predisposition syndromes as a function of age, with tumors often diagnosed in the first decade of life.[12] The rate of progression of adenomas among BMMRD patients appears to be accelerated and more rapid than in LS. This may occur because BMMRD tumors acquire early somatic mutations in the polymerase proofreading genes *DNA polymerase ε* and *δ* (*POLE* and *POLD1*), and together with the underlying DNA-MMR defect, develop ultrahypermutated tumors with a massive number of substitution mutations and an unprecedented rate of progression.[13] This contrasts with the distinctly smaller numbers of mutations seen in most childhood malignancies compared with adult-onset cancers.[14]

In view of the striking cancer and mortality risk in these patients, close surveillance of affected individuals is important for early cancer detection. Over the past 15 years, BMMRD patients have been followed up with a clinical surveillance protocol[15] designed to diagnose tumors in asymptomatic patients amenable to surgical resection. Gastrointestinal and brain tumors are the most common malignancies described in BMMRD, occurring in more than half of these patients.[16-18] Unfortunately, no consensus exists on the optimal screening and surveillance guidelines, which confounds managing physicians, and can lead to inappropriate refusal to pay for reasonable care by insurers.

BMMRD will occur in 25% of the offspring of 2 individuals who have LS involving the same gene; consequently, BMMRD is quite rare. The mutations may be homozygous or compound heterozygotes, and the various combinations of mutations can lead to clinical pleiotropy. Patients with colon cancer and café-au-lait macules presumed to have familial adenomatous polyposis with no APC mutation identified should be re-evaluated for BMMRD.[19]

BMMRD probably is under-recognized. Moreover, the rarity of this disease, accompanied by childhood presentation, has led to limited research and the absence of controlled trials in the management of this disorder. Nevertheless, clinicians are confronted with difficult management decisions without guidelines based on data or consensus. Consequently, several experts have pooled collective experiences to develop consensus guidelines as an initial attempt to identify more uniform approaches to patient management, and to prioritize areas in greatest need of research.

DIAGNOSTIC CHALLENGES IN BMMRD

BMMRD is an under-recognized syndrome with pleiotropic presentations. Clues to guide clinicians to suspect BMMRD and increase recognition of BMMRD are included in Table 2. Patients may be children or young adults diagnosed with early onset CRC, brain tumors, leukemias, lymphomas, or uterine cancer. Any child or young adult with cancer plus parental consanguinity or features of neurofibromatosis not explained by other confirmed germline mutations should be suspected. Raising