Constitutional mismatch repair-deficiency syndrome

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(Related Original Article on page 851)

The mismatch repair (MMR) machinery contributes to genome integrity and the *MLH1*, *MSH2*, *MSH6* and *PMS2* genes play a crucial role in this process. MMR corrects single base-pair mismatches and small insertion-deletion loops that arise during replication. Moreover, the MMR system is involved in the cellular response to a variety of agents that damage DNA[1] and in immunoglobulin class switch recombination.[2] Heterozygous germline mutations in *MLH1*, *MSH2*, *MSH6* and *PMS2* cause Lynch syndrome (LS), an autosomal dominant cancer syndrome associated with hereditary nonpolyposis colorectal cancer (HNPCC), endometrium carcinoma and other malignancies, occurring on average in the fourth and fifth decade of life. Notably, LS associated tumors display somatic loss of the remaining wild type *MLH1*, *MSH2*, *MSH6* or *PMS2* allele and evidence of microsatellite instability (for review see [3]).

In contrast to individuals with LS who harbor a heterozygous mutant MMR gene allele, rare cases with biallelic deleterious germline mutations in MMR genes leading to constitutional mismatch repair-deficiency (CMMR-D) have been recognized since 1999.[4,5] This cancer syndrome is characterized by a broad spectrum of early-onset malignancies and a phenotype that resembles neurofibromatosis type 1. In this issue of Haematologica, Ripperger and colleagues report on a patient with CMMR-D caused by a novel *MSH6* mutation leading to a T-cell lymphoma and colonic adenocarcinoma at six and 13 years of age, respectively. In addition, they review 26 leukemia and/or lymphoma cases reported previously.[6]

The clinical presentation and tumor spectrum of CMMR-D

Our knowledge of the CMMR-D syndrome originates primarily from the medical literature; consequently, potential publication bias must be kept in mind as we interpret these reports. Table 1 summarizes the malignancies observed in 89 reported[6-11] and 3 unreported cases of CMMR-D. Neoplasms can be divided into four groups: (1) hematologic malignancies (reviewed in [6]); (2) brain tumors; (3) LS-associated tumors; and (4) other malignancies. Notably, 31 out of the known 92 CMMR-D patients developed more than one malignancy, and in 19 cases the second or third neoplasm was an LS-associated tumor.

In some cases of CMMR-D, areas of skin hypo-pigmentation have been reported.[12-15] However, signs reminiscent of neurofibromatosis type 1 (NF1), in particular café-au-lait macules (CALMs), are much more common and were observed in the majority of the reported cases (63/92). There are only 2 patients explicitly reported to lack CALMs or other signs of NF1.[9,13] Interestingly, several reports stress that CALMs in patients with CMMR-D differ from typical NF1-associated CALMs in that they vary in their degree of pigmentation, have irregular borders, and may display a segmental distribution. Other features of NF1 found in CMMR-D patients include skinfold freckling, Lisch nodules, neurofibromas and tibial pseudarthrosis. Hence, it is not surprising that a number of CMMR-D cases were initially diagnosed as having NF1. It has been speculated that the NF1-like clinical features in CMMR-D result from germline mosaicism arising early during embryonic development. The identification of a truncating *NF1* mutation in the blood of one patient[16] and data supporting the notion that the *NF1* gene is a mutational target of MMR deficiency[17] are in line with this assumption. However, extensive mutation analysis in other CMMR-D patients has not confirmed this theory (see [8,12,18] and papers cited therein).

Péron *et al.*[2] have shown in 3 CMMR-D patients that

Table 1. List of malignancies in 92 CMMR-D patients.

Malignancies	N. of malignancies	Median age at diagnosis (years) (range)
Hematologic malignancies		
Non-Hodgkin's and other lymphoma	19	6 (0.4-17)
Acute lymphoblastic leukemia	6	5 (2-15)
Acute myeloid leukemia	3	9 (6-10)
Atypical chronic myeloid leukemia	1	1
Acute leukemia	1	2
Total	30	6 (0.4-17)
Brain tumors		
Glioblastoma and other astrocytic tumors	32	9 (2-35)
Supratentorial primitive neuroectodermal tumor	5	8 (4-14)
Medulloblastoma	4	7 (6-7)
Unspecified	3	23 (4-24)
Total	44	8 (2-35)
Lynch syndrome-associated tumors		
Colorectal cancer	37	16 (8-35)
Duodenum/jejunum/ileum cancer	9	26 (11-42)
Endometrial cancer	5	24 (23-31)
Ureter/renal pelvis cancer	1	15
Total	51	18 (8-42)
Others		
Neuroblastoma	1	13
Wilms tumor	1	4
Rhabdomyosarcoma	1	4
Ovarian neuroectodermal tumor	1	21
Infantile myofibromatosis	1	1
Breast cancer	1	35
Sarcoma	1	65

Multiple synchronosous colorectal cancers were counted only once.

constitutional *PMS2* deficiency leads to impaired immunoglobulin class switch recombination characterized by increased serum IgM concomitant with decrease or absence of IgG2, IgG4, and IgA. Of note, one CMMR-D patient initially presented with a primary immunodeficiency,[2] and patients with biallelic *MSH2* and *MSH6* mutations also show IgG2 and/or IgA deficiency [15,19,20]. It remains to be seen whether defective IgA and IgG production is a common feature of CMMR-D. Fortunately, severe bacterial infections have not been reported to occur at high frequencies in persons with CMMR-D.

Genotype-phenotype correlation of CMMR-D

A review of the literature suggests that the clinical features in patients with biallelic germline mutations of *MLH1* or *MSH2* differ from those with biallelic germline mutations of *MSH6* or *PMS2* (Table 2). Hematologic malignancies appear to occur more frequently in patients with *MLH1* or *MSH2* mutations than in patients with mutations of *MSH6* or *PMS2*. In contrast, the latter group appears to have a higher prevalence of brain tumors. Furthermore, tumors tend to develop earlier in *MLH1* or *MSH2* mutation carriers than in patients with a mutation of *MSH6* or *PMS2*. Patients with biallelic mutations in *MSH6* or *PMS2* are more likely to survive their first tumors and develop a second malignancy. Overall, the prevalence of LS-associated tumors is higher in patients with biallelic *MSH6* or *PMS2* mutations than in biallelic *MLH1* or *MSH2* mutation-positive individuals (Table 2). These factors facilitate the clinical diagnosis of CMMR-D in patients with mutations of *MSH6* or *PMS2* and may at least partly explain the preponderance of *PMS2* mutations in published cases.

Strategies for clinical and subsequent molecular diagnosis of CMMR-D

In view of the wide tumor spectrum that overlaps with Lynch and Turcot syndrome but also includes hematologic malignancies and embryonic tumors such as neuroblastoma, Wilms tumor and rhabdomyosarcoma (Table 1), CMMR-D should be considered in the differential diagnosis in all patients with malignancies (except clearly NF1-associated tumors) who show one or more of the following features: (1) CALMs and/or other signs of NF1 and/or hypo-pigmented skin lesions; (2) consanguineous parents; (3) family history of LS-associated tumors; (4) second malignancy; and (5) sibling with childhood cancer. It is important to note that especially in patients with *PMS2* mutations, the family history will often not fulfill the Amsterdam or revised Bethesda criteria for LS.

Typically, confirmation of the diagnosis involves the analysis of microsatellite instability (MSI) and/or immunohistochemistry (IHC), followed by mutation analysis. MSI analysis follows current protocols used for LS-screening; however, this analysis may be unreliable in CMMR-D related brain tumors.[7,11,21] IHC is a useful technique employed in patients with CMMR-D associated neoplasms including brain tumors and guides subsequent mutation analysis in the four MMR-genes. In general, a truncating mutation in *PMS2* or *MSH6* will result in isolated loss of these proteins, whereas a mutation in *MLH1* or *MSH2* will lead to concurrent loss of MLH1/PMS2 or MSH2/MSH6, respectively, since *MLH1* and *MSH2* are the obligatory partners in the formation of MLH1/PMS2 and MSH2/MSH6 heterodimers. Notably, in the case of an underlying missense mutation, IHC may show normal results. As CMMR-D patients constitutively lack the expression of one of the MMR genes, IHC detects loss in both neoplastic and non-neoplastic tissues. Conveniently, expression loss of one of the MMR genes can be demonstrated in blood lymphocytes (e.g. by Western blot [2]). Similarly, it has been shown that MSI can be determined in normal non-neoplastic tissue of CMMR-D patients by analyzing DNA samples that are diluted to approximately 0-3 genome equivalents per PCR-reaction.[22] Nonetheless, standardized procedures for the detection of MMR expression loss and MSI in non-neoplastic tissue from CMMR-D patients have not been developed to date. The diagnosis of CMMR-D should be confirmed by gene-specific mutation analysis. Reliable methods for all four MMR genes including *PMS2* are now available.[12] Mutation analysis will facilitate identification and surveillance of heterozygous and homozygous individuals in the wider family, and allow for informed decision-making about prenatal or pre-implantation genetic diagnosis.

Treatment and surveillance of the patient and counseling of relatives

Genetic counseling should be offered to the parents prior to testing of the affected child, and should include information on the potential 25% recurrence risk and on the clinical consequences of a possible heterozygous mutation in both parents. Predictive testing following the established interdisciplinary counseling guidelines should be offered to all family members once a mutation has been identified. Heterozygous family members should be followed according to current LS-guidelines.[23]

Because of the wide spectrum of malignancies in CMMR-D patients, defining recommendations for surveillance of affected patients remains a challenge. Early diagnosis of CMMR-D and subsequent cancer screening at regular intervals may increase the likelihood of detecting associated cancers, such as colon cancer or brain tumors, at an operable stage. In theory, this screening could

Table 2. Differences in the overall tumor spectrum and age of malignancy onset between carriers of biallelic *MLH1/MSH2* and *MSH6/PMS2* mutations, respectively.

Genes	N. of patients (families)	Tumor type				Median age at diagnosis of primary tumor (range)	N. of patients with a second malignancy
		hematologic	brain	LS-associated	others		
MLH1/MSH2	24 (14)	11 (46%)	8 (33%)	7 (29%	3 (12%)	4y (0.4y-35y)	5 (20%)
MSH6/PMS2	65 (39)	19 (29%)	36 (55%)	44 (68%)	4 (6%)	9y (1y-31y)	26 (40%)

LS: Lynch syndrome.

include regular exams such as: (1) clinical evaluation; (2) blood tests with full blood count and carcinoembryonic antigen (CEA); (3) magnetic resonance imaging of the brain; (4) endoscopic examination of the gastrointestinal tract; and (5) endometrial sampling and transvaginal ultrasound for endometrial and ovarian cancer. However, these recommendations rest only on clinical judgment and do not represent a standard of care. To date there is no available evidence to support any of these recommendations or to provide guidance on the optimal frequency of such tests. Likewise, there is currently no information available regarding the optimal treatment of CMMR-D patients. Several reports stress that careful attention should be given to the possibly increased cyto-toxicity and reduced efficacy of chemotherapeutic agents due to constitutionally impaired mutation repair, and the high risk of a second malignancy [6,8,14,15].

Reports such as the article by Ripperger and colleagues are valuable in increasing awareness and knowledge of the syndrome in the clinical community. Nevertheless, systematic studies are needed in order to better define the phenotype of MMR-D. Data related to cancer screening, treatment and outcome should be collected and evaluated systematically to provide a basis for recommendations on how to manage patients with CMMR-D.

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