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Case Report

Cancer and constitutional Mismatch Repair Deficiency syndrome due to homozygous MSH 6 mutation in children with Café au Lait Spots and review of literature

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ABSTRACT

Background. Constitutional mismatch repair deficiency (CMMRD) syndrome is a rare childhood cancer predisposition syndrome resulting from biallelic germline mutations of mismatch repair (MMR) genes. CMMRD syndrome is characterised by early onset malignancies in children.

Case. Here we present affected children of consanguinous parents diagnosed with CMMRD syndrome due to germline bi-allelic MSH 6 gene mutations with café au lait spots and multiple family cancers from Turkey and reported cases with CMMRD syndrome associated MSH 6 mutation in English literature. Hence, we reviewed English literature from 1990 to 2020 using Pub-Med database. Keywords used to search included constitutional mismatch repair deficiency syndrome, childhood cancer and MSH 6 gene mutation.

Conclusions. We emphasize that the inclusion of CMMRD syndrome in the differential diagnosis of a patient who presents with cafe´ au lait spots and/or hypopigmented skin lesions and cancer especially when consanguinity and/or a history of cancer coexist in children.

Key words: childhood cancer, constitutional mismatch repair deficiency syndrome, MSH 6 mutation.

Constitutional mismatch repair deficiency (CMMRD) syndrome is a rare childhood cancer predisposition syndrome resulting from biallelic germline mutations of the DNA mismatch repair (MMR) genes.[1] It is associated with a wide spectrum of malignancies including hematological, brain and intestinal tumors. It also frequently mimics clinical features of neurofibromatosis type 1 (NF1).[2-4] Although bi-allelic mutations in genes that regulate DNA mismatch repair, including MLH1, MSH2, MSH6 and PMS2 causes CMMRD syndrome, monoallelic germline mutations in one of these genes cause Lynch syndrome.[4-6] Therefore, individuals with bi-allelic mutations have a dysfunctional mismatch repair system from birth, CMMRD syndrome is characterised by early onset malignancies.[7-10] Hence, wreviewed English literature from 1990 to 2020 using Pub-Med database. Keywords used to search included constitutional mismatch repair deficiency syndrome, childhood cancer and MSH 6 gene mutation. Here we present affected children of consanguinous parents diagnosed with CMMRD syndrome due to germline bi-

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allelic MSH 6 gene mutations with café au lait spots and multiple family cancers from Turkey and reported cases with CMMRD syndrome associated MSH 6 mutation in English literature.

Case Report

A 8-year-old female was admitted to our clinic with diagnosis of a brain mass. In her past history; she was followed up with the diagnosis of NF-1 and familial mediterranean fever. Her parents were first-degree cousins with multiple cancer histories: one brother died from medulloblastoma and metachronous colon adenocarcinoma at 15 years of age and one sister died from brain tumor at 4 years of age. In addition, parents' uncle and aunt had colon adenocarcinoma and thyroid papillary cancer at 45 and 50 years of age, respectively. On physical examination, 8 to 10 cafe´ au lait spots and hypopigmented skin lesions with irregular borders on her body were found. Other findings of neurofibromatosis type 1 including neurofibromas, Lisch nodules, tibia pseudoarthrosis, sphenoid wing dysplasia, and optic glioma were not seen. Laboratory investigation was within normal limits other than low serum Ig G2 levels. Cranial magnetic resonance imaging (MRI) showed a partially enhancing mass (21x34x22mm) in the left cerebellar region, nonspesific subcortical white matter T2-FLAIR hyperintensities in frontal and parietal lobes. Also, the focal areas of hyperintense signal intensity in bazal ganglia, thalamus, mesencephalon and venous anomaly were noted. She underwent near-total resection of cerebellar mass and histopathology revealed classic desmoplastic medulloblastoma. The post-operative craniospinal MRI showed a left cerebellar hyperintensity (12x21mm) and enhancing lesion (4x8mm) without nodularity associated with recent surgery and other nonspesific intracranial findings were the same as the previous MRI. The index case was administered craniospinal irradiation (54 Gy) with a diagnosis of Medulloblastoma (Stage M2) according to Chang staging system followed by chemotherapy consisting of CCNU, cisplatin and vincristine. Because of positive family history and café au lait spots of the index case, we proceeded with genetic analysis that disclosed a novel homozygous single base insertion mutation in exon 5 of the MSH 6 gene (c.3261dupC p. Phe10881Leufs*5) (Fig. 1). NF type I and II genes were normal.

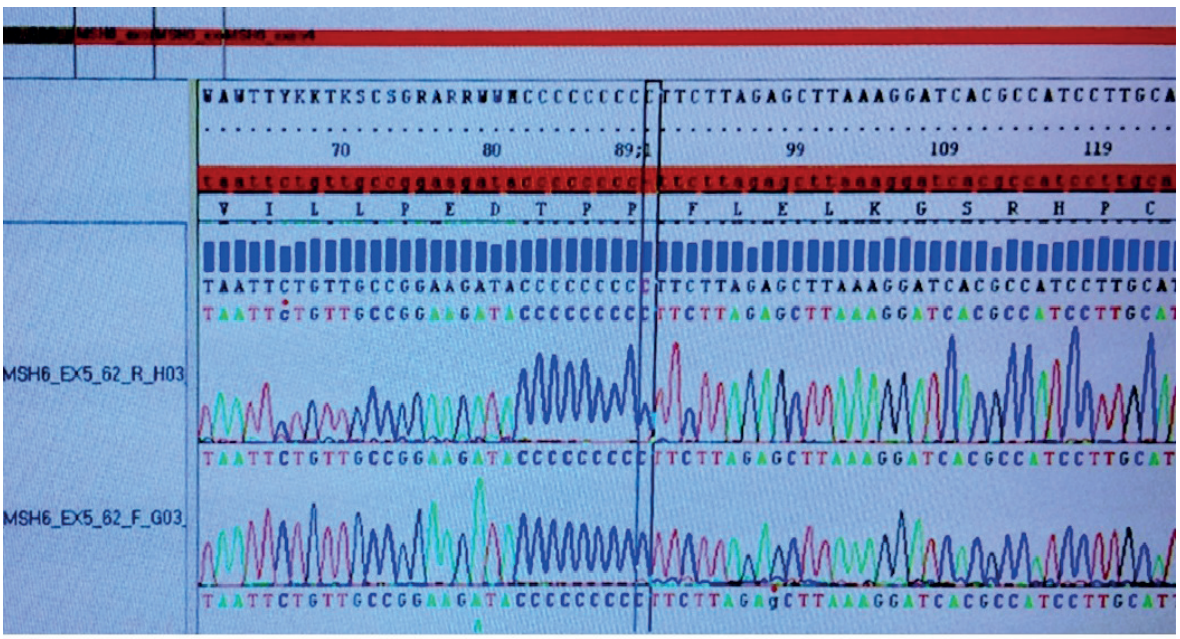

Fig. 1. MSH6 Gene Mutation of Index Case

The genetic screening of family members were performed for MSH 6 gene mutation. The family history is shown in the pedigree in Figure 2. After 5 cycles of conventional chemotherapy, the family declined the chemotharapy due to severe hematologic toxicities and recurrent infectious complications. The colonoscopy which was normal previously revealed a new occurance of colonic tubulovillous adenomas. The chemotherapy was stopped and anti-programmed death-1 (Anti-PD-1) drugs (nivolumab; 3 mg/kg/dose, every 2 weeks) were given for 24 doses. During the anti-PD-1 treatment, neuroimaging findings were stable and colonic polyps were gradually decreased in number and size. One year after the end of the treatment with anti-PD-1, MRI showed a new occurance of a right cerebellar heterogenously enhancing mass (33x41x28mm) with restricted diffusion causing midline shift. Also, colonoscopy revealed new colonic polyps. She underwent tumor resection but died post-operatively. Histopathology revealed medulloblastoma. Informed consent was received from the family.

Discussion

CMMRD is considered in children with glioma, leukemia, colorectal cancer and other hereditary nonpolyposis colon cancers and any of the findings: 1) cafe´ au lait spots and/or hypopigmented skin lesions 2) history of parental consanguinity, or 3) positive family

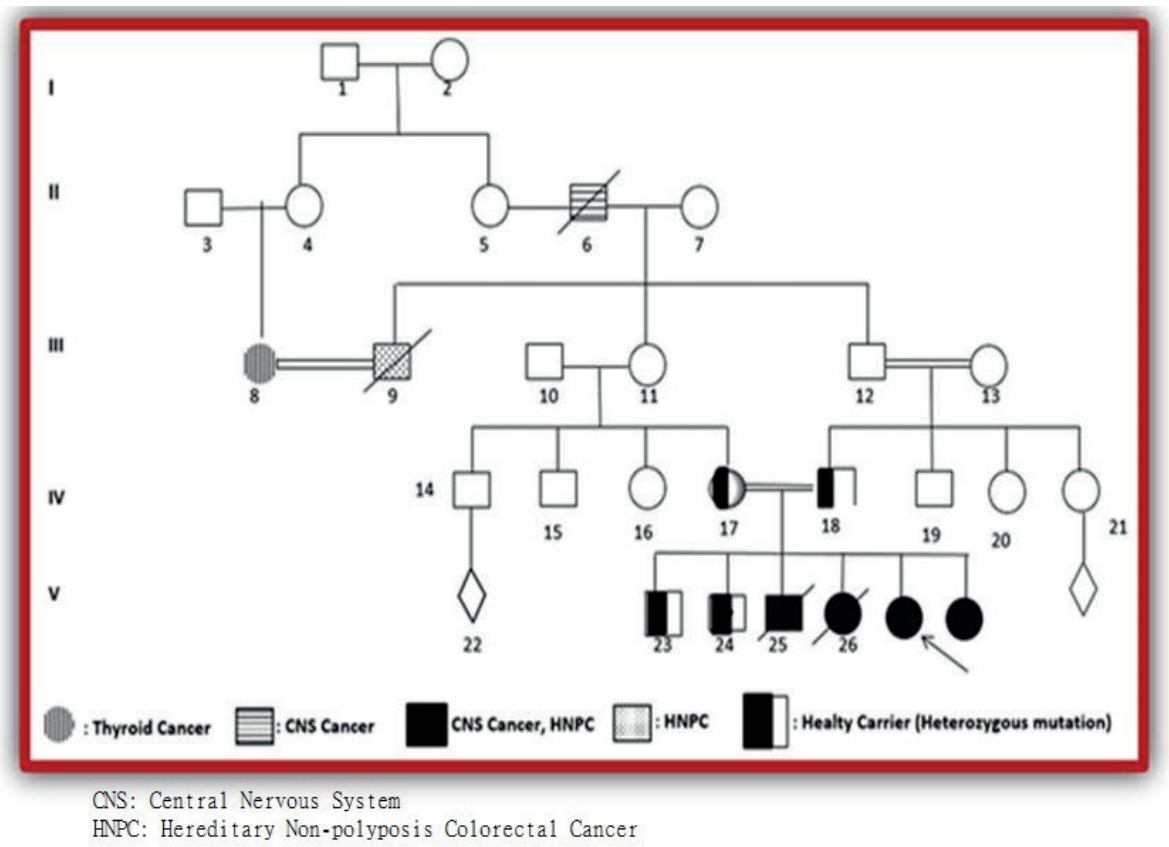

Fig. 2. Five generation family tree representing cases with MSH6 mutation and/or cancers: Parents and two siblings (11 and 6years old males) are heterozygous; Sibling six-month-old is homozygous; 15-year-old deceased sibling with medulloblastoma and metastatic colorectal carcinoma was homozygous for MSH6 mutation; Other 4-year-old deceased sibling with brain tumor has no genetic test. CNS: Central Nervous System; HNPC: Hereditary Non-polyposis Colorectal Cancer

history of hereditary nonpolyposis colon cancers. In addition, a three-point scoring system for the suspected diagnosis of CMMRD in a pediatric/young adult cancer patient has been recommended by European Consortium Tumours highly specific for CMMRD syndrome.[9,11,12]

The global prevalence of CMMRD is currently unknown, but rate is expected to increase in regions with a high prevalence of consanguineous marriages in especially low and middle income countries. Recently, a modified surveillance protocol for these countries with limited resources has been reported. This surveillance protocol consisted of complete blood count and fecal occult blood every 6 months, upper endoscopy/ colonoscopy and abdominal ultrasound annually, and brain MRI or CT every 6 months in children. In addition, whole body MRI was advised for surveillance as recommended in developed countries where it is available and/or reimbursed.[13]

According to a review of 146 cases of CMMRD syndrome conducted by Wimmer et al[9], the most common mutation was PMS2 mutations (60% of cases). Twenty-two percent and 20% of cases are caused by MLH1 or MSH2 and MSH6 mutations, respectively.[9]

We reviewed English literature from 1990 to 2020 using Pub-Med database. Keywords used to search included constitutional mismatch repair deficiency syndrome, childhood cancer and MSH 6 mutation. We could find approximately 38 patients diagnosed with CMMRD syndrome due to MSH 6 mutations among 20 cases and/or case series from 63 articles. The characteristics of the 38 pediatric patients with CMMRD syndrome including our patients are shown in Table I.[1,12-31] The median age of onset of the first tumour was 8 years (range, 1 to 17 years). The 38 individuals with CMMRD had a total of 66 tumours (Table I). Nineteen patients had one malignancy, 13 patients had two malignancy and 7 patients had more than two malignancy. Of the 66 tumors 28 (42%) were brain tumours, 15 (23%) haematological malignancies, 19 (29%) GI poliposis and/or colon cancer, and 4 (6%) other tumours. Among the CNS tumours, the most prevalent type were glioblastoma multiforme and other high grade glial tumors (n:20; 71%). On the other hand, we found a limited number of medulloblastoma cases (n:5;25%) in patients with CMMRD with MSH6 gene mutations including with our patient.

The cafe´ au lait spots and/or hypopigmented skin lesions mimicking NF 1 features were determined in 29 patients diagnosed with CMMRD syndrome including with our patients in Table I. The cafe´ au lait spots and/ or hypopigmented skin lesions history of seven patients were not available. The cafe´ au lait spots in patients with CMMRD usually differ in colour and shape from typical NF1-associated cafe au lait spots. Regardless of the genetic basis underlying clinical findings in patients with CMMRD, the majority presented cafe au lait and/or other signs indicative NF 1, although a minority fullfilled the NIH criterion for NF 1 diagnosis.[2] This phenotypic overlap caused to misdiagnosis of CMMRD patients as having NF1 and impeded proper management and genetic counselling of these patients and their families similar to our patients in the past. As reported case and case series of CMMRD syndrome increase, misdiagnosis of these cases will be less in the future.

CMMRD syndrome is an autosomal recessive cancer predisposition syndrome resulting from bi-allelic mutations in MMR genes. Although consanquinity is highly suggestive for CMMRD syndrome, it can be seen in non-consanquineous families usually as compound heterozygous mutations.[11] In the present review, there were consanquinity in 22 patients (58) including our patient. The consanguinity history of seven patients were not available.

Immunotherapies are directed against inhibiting receptors, such as PD-1 protein and one of its ligands programmed death-ligand 1 (PD-L1). Nivolumab, is anti-PD-1 mAb, binds PD-1 and stimulates memory response to tumor antigen-specific T cell proliferation.[3]

Table I. The clinical features and tumors of patients with CMMRD.

Reference	First tumor (age)	Second tumor (age)	Third tumor (age)	Fourth tumor (age)	Features	Family history
Menko et al [14] 2004	Oligodendroglioma (10y)	CRC (12y)			CAL	Consang. Family cancer was positive
Hedge et al [15] 2005	Lymphoma (5y)	CRC (8y)			CAL	No Consang. Family cancer was positive
	GBM (8y)				CAL	No Consang. Family cancer was positive
Ostergaad et al [16] 2005	Pilocytic astrocytoma (9y)	Anaplastic astrocytoma(10y)	T-cell lymphoma (10y)		CAL, frecklesIg A deficiency	No Consang. Family cancer was positive
	Spinal glioblastoma (3y)				CAL, frecklesIg A deficiency	No Consang. Family cancer was positive
Scott et al [17] 2007	Medulloblastoma (7y)	AML (10y)	CRC (13y)		CAL,2 hairy nevus, hypopigm. macules IgA and G2 deficiencies	Consang. Family cancer was positive
Poley et al [18] 2007	NHL (4y)	Anaplastic oligodendroglioma (6y)			CAL	Consang. Family cancer was positive
Auclair et al [19] 2007	GI polyposis/CRC (9y)				CAL, Lisch nodules	Consang. Family cancer was positive
Etzler et al [20] 2008	Medulloblastoma (6 y)	MDS/AML (9 y)			CAL	Consang. Family cancer was positive
	GBM (9 y)				CAL, hypopigm. macules	Consang. Family cancer was positive
Rahner et al [21] 2008	CRC (17 y)				SLE, vitiligo	No Consang. No Family cancer
Peter et al [22] 2009	T-cel lymphoma (8y)				CAL, lisch nodules	No Consang. Family cancer was positive
Ripperger et al [23] 2010	T-cell lymphoma (6y)	CRC (13 y)			CAL	Consang. Family cancer was positive

AML: acute myeloblastic leukemia, CAL: café-au-lait, Consang: consanguinity, CRC: colorectal cancer, Hypopigm: hypopigmented, TLL: T-cell lymphoblastic lymphoma, GBM: glioblastoma multiforme, SLE: systemic lupus erythematosus, GI: gastrointestinal, mo: mounts, WT: Wilms tumor, NA: not available

Table I. Continued.

Reference	First tumor (age)	Second tumor (age)	Third tumor (age)	Fourth tumor (age)	Features	Family history
Ilencikova et al [24] 2012	Gliomatosis cerebri (11y)	T-cell lymphoma (11y)			CAL	Consang. Family cancer was positive
Hoel et al [25] 2014	T-cell lymphoma (20 mo)	CRC (13 y)			No CAL	Consang. No Family cancer
Bougard et al [26] 2014	GI polyposis (14y)	CRC (17y)	CRC (19y)	Urinary tract carcinoma (24y)	CAL	Consang. Family cancer was positive
Bakry et al [12] 2014	T cell lymphoma (10 y)	GI polyposis (12.5y)	GBM (8y)		CAL	Consang. No Family cancer
	Anaplastic olygodendroglioma (10y)				CAL	Consang. Family cancer was positive
	Anaplastic astrocytoma (11y)				CAL	Consang. Family cancer was positive
	GI polyposis (11y)				CAL	No Consang. No Family cancer
	T-cell lymphoma (6 y)	GI polyposis (11y)			CAL, freckles	No Consang. No Family cancer
	GBM (12,5y)				CAL	No Consang. No Family cancer
El-Hasid et al [27] 2015	AML (26 mo)				CAL, hypopigm. macules	Consang. No Family cancer
Lovaine et al [1] 2015	GBM (6y)				CAL	Consang. Family cancer was positive
	CRC/polyp (11y)				CAL	Consang. No Family cancer
	T-cell lymphoma (6y)	T-cell lymphoma (11y)	GBM (14y)	CRC /polyps (14y)	CAL, hypopigm. macules	Consang. No Family cancer
Al Harbi et al [28] 2018	GBM (5y)				CAL	Consang.Family history was positive

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Table I. Continued.

Reference	First tumor (age)	Second tumor (age)	Third tumor (age)	Fourth tumor (age)	Features	Family history
Citak et al [29] 2019	WT (2y)	GBM (4y)	T-ALL (6y)		CAL, inguinal freckling	Consang. No Family cancer
Athanasiadis et al [30] 2020	GBM (13y)	CRC (13y)			CAL	Consang. Family cancer was positive
Our patients	Medulloblastoma (8y)	GI polyposis (9)			CAL, hypopigm. macules Ig G2 deficiency	Consang. Family cancer was positive
	Medulloblastoma (12y)	CRC (13 y)			CAL, hypopigm. macules freckles	Consang. Family cancer was positive
Guerrini-Rousseau L et al [31]	High grade glioma (11y)				NA	NA
	High grade glioma (13y)				NA	NA
	Medulloblastoma (7y)	CRC (22)	High grade glioma (25y)		NA	NA
	High grade glioma (17y)				NA	NA
	Medulloblastoma (1y)				NA	NA
	High grade glioma (3y)				NA	NA
	High grade glioma (13y)	High grade glioma (13y)			NA	NA

AML: acute myeloblastic leukemia, CAL: café-au-lait, Consang: consanguinity, CRC: colorectal cancer, Hypopigm: hypopigmented, TLL: T-cell lymphoblastic lymphoma, GBM: glioblastoma multiforme, SLE: systemic lupus erythematosus, GI: gastrointestinal, mo: mounts, WT: Wilms tumor, NA: not available

The optimal duration of immunotherapy is unknown, especially in the pediatric setting. Because the clinical findings remained stable in our index patient, nivolumab was stopped after 24 doses. Immunotherapy using immune checkpoint inhibitors have shown great promise in both adult and pediatric malignancies. First remarkable and durable responses reported were from two siblings with CMMRD-associated recurrent multifocal glioblastoma whom were treated with nivolumab (immune checkpoint inhibitor).[6] After that, another study reported a 5-year-old female with CMMRD and relapsed glioblastoma multiforme whom was treated with nivolumab had durable response.[28] Recently, the European C4CMMRD consortium has reported that the outcome of patients with constitutional mismatch repair deficiency (CMMRD) and brain tumor from the C4CMMRD database. According to their report, 8 patients with high grade glial tumor were administered immunotherapy with anti-PD1 antibodies at relapse. They observed disease progression in 7 of these patients within the first two months of immunotherapy and 6 of them died at 5.2 months (ranges between 1.8–9.5months) after the first injection. Therefore, they concluded that the prognosis of patients with a CMMRD-related brain tumor (especially glioblastoma) is not as good as originally thought.[31]

Although significant progress has been made about cancer immunotherapy, there is no sufficient experience with prophylactic immunotherapy to prevent cancer formation especially in cancer predisposing syndrome in childhood. Because the surveillance does not quarantee detection of precancerous lesions or cancer at a curable stage, it causes a great psychological burden in families who have children with homozygous MMR gen mutations. Recently, cancer immunoprevention has been emphasized especially for healthy cases with homozygous mutation of MMR genes during surveillance to decrease the tumorogenesis.[32,33]

In conclusion, CMMRD syndrome is a rare and challenging disease. Because of the dismal prognosis of after cancer occurance, further studies are required to prevent cancer with immunotherapy in patients with CMMRD syndrome. In addition, we emphasize the inclusion of CMMRD syndrome in the differential diagnosis of a cancerous patient who present with cafe´ au lait spots and/or hypopigmented skin lesions especially when consanguinity and/or a history of family cancer coexist in children.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: DÖ; data collection: DÖ; analysis and interpretation of results: DÖ, EUC; draft manuscript preparation: DÖ, EUC, NT, FP, EUC, NT, FP, AOE, SH, AYE, AMD. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

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