Intensive surveillance endoscopy for multiple gastrointestinal tumors in a patient with constitutional mismatch repair deficiency: case report

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Abstract
Background: Constitutional mismatch repair deficiency (CMMRD) is an extremely rare autosomal recessive hereditary disease characterized by the absence of mismatch repair gene activity from birth, which results in brain tumors, colonic polyposis, gastrointestinal cancers, and lymphomas later in life. An aggressive approach, including colectomy or proctocolectomy, is recommended for the treatment of colorectal cancer. Additionally, partial colectomy with subsequent endoscopic surveillance may be an alternative strategy due to poor patient's condition, although there is no evidence of surveillance endoscopy after partial colectomy for CMMRD.

Case presentation: A 13-year-old male patient with a history of T-lymphoblastic lymphoma underwent total gastrointestinal endoscopy, which revealed rectal cancer, colorectal polyposis, and duodenal adenoma. Differential diagnosis included constitutional mismatch repair deficiency according to its scoring system and microsatellite instability, and subsequent germline mutation testing for mismatch repair genes confirmed the diagnosis of constitutional mismatch repair deficiency based on a homozygous mutation in mutS homolog 6 (MSH6). The patient and his family refused colectomy due to the high risk of malignancies other than colorectal cancer, which could require radical surgery. Therefore, the patient underwent low anterior resection of the rectosigmoid colon for rectal cancer and intensive surveillance endoscopy for the remaining colon polyposis. During the 3-year period after initial surgery, 130 polyps were removed and the number of polyps gradually decreased during 6-months interval surveillance endoscopies, although only one polyp was diagnosed as invasive adenocarcinoma (pT1).

Conclusions: Our experience of short surveillance endoscopy illustrates that this strategy might be one of options according to patient's condition.

Keywords: Colorectal polyposis, Constitutional mismatch repair deficiency, Surveillance endoscopy, Lynch syndrome, Case report

Background
Lynch syndrome is a cancer predisposition syndrome caused by heterozygous germline mutations in DNA mismatch repair (MMR) genes, including mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), MSH6, PMS1
Additionally, one duodenal adenoma, 10 mm in size, was identified by esophagoduodenoscopy and capsule endoscopy. Serum levels of immunoglobulin G and G4 were 434 (normal, 870–1700) and < 2.0 (normal, 11–121) mg/dL, respectively.

CMMRD was considered in the differential diagnosis based on these findings and the CMMRD scoring system, although the patient did not fulfill the Amsterdam criteria for Lynch syndrome (Fig. 1D) [8, 9]. Therefore, testing after obtaining informed consent revealed the rectal cancer harbored high microsatellite instability. After obtaining further written informed consent, subsequent genetic testing performed for hereditary colorectal cancer syndromes, including those associated with mismatch repair genes (MLH1, MSH2, PMS2, and MSH6), adenomatous polyposis coli, and mutYH-associated polyposis revealed one homozygous frame shift mutation in MSH6 (NM_000179.2; c.3261del p.Phe1088SerfsTer2), which was reported as pathogenic (ClinVar accession VCV000089363.14, https://www.ncbi.nlm.nih.gov/clinvar/, last accessed May 15, 2021), confirming the diagnosis of CMMRD (Fig. 2A). Genetic testing showed that the patient’s mother and father were heterozygous carriers of the MSH6 c.3261del mutation, leading to the diagnosis of Lynch syndrome based on the same germline mutation in both parents (Fig. 3A, B). Both parents had normal findings by colonoscopy and esophagoduodenoscopy.

The patient and his parents were carefully and repeatedly informed about the risks and benefits of colectomy and proctocolectomy for rectal cancer and colorectal polyposis, which they declined because of the high risk of small intestinal and non-gastrointestinal cancers in future. Therefore, the patient underwent low anterior resection (LAR) of the rectosigmoid colon for rectal cancer and surveillance endoscopy was planned for the remaining colon polyposis and duodenal adenoma. Histopathologically, the excised rectal mass was an intramuscosal, moderately differentiated tubular adenocarcinoma (pTis) in tubulovillous adenoma without lymph node metastasis. The patient was diagnosed with Stage I rectal cancer according to the Tumor-Node-Metastasis staging system (Fig. 2C–F). After surgery, colonoscopy was planned with the following goals: (1) polypectomy every 4–6 months until only polyps sized < 4 mm remained; (2) histological evaluation of polyps sized > 10 mm and polyps sized < 10 mm with suspicion of cancer based on endoscopic appearance [10].

**Case presentation**

A 6-year-old boy was diagnosed with T-lymphoblastic lymphoma and received chemotherapy and radiotherapy; he achieved complete remission and underwent annual follow-up with positron emission tomography/computed tomography (CT) using 18-fluoro-2-deoxyglucose. At the age of 13, he was referred to our department for further evaluation of a rectal tumor identified by positron emission tomography/CT.

Physical examination revealed several café au lait macules and multiple cutaneous hemangiomas. Abdominal enhanced CT revealed irregular rectal wall thickening without lymphadenopathy or distant metastases (Fig. 1A–C). Total colonoscopy and endoscopic biopsy revealed a 45-mm sessile adenocarcinoma with a central depression in the rectosigmoid area and more than 100 adenomatous polyps, 2–15 mm in size, distributed throughout the colon and rectum (Fig. 2A, B). Additionally, one duodenal adenoma, 10 mm in size, was identified by esophagoduodenoscopy and capsule endoscopy. Serum levels of immunoglobulin G and G4 were 434 (normal, 870–1700) and < 2.0 (normal, 11–121) mg/dL, respectively.

CMMRD was considered in the differential diagnosis based on these findings and the CMMRD scoring system, although the patient did not fulfill the Amsterdam criteria for Lynch syndrome (Fig. 1D) [8, 9]. Therefore, testing after obtaining informed consent revealed the rectal cancer harbored high microsatellite instability. After obtaining further written informed consent, subsequent genetic testing performed for hereditary colorectal cancer syndromes, including those associated with mismatch repair genes (MLH1, MSH2, PMS2, and MSH6), adenomatous polyposis coli, and mutYH-associated polyposis revealed one homozygous frame shift mutation in MSH6 (NM_000179.2; c.3261del p.Phe1088SerfsTer2), which was reported as pathogenic (ClinVar accession VCV000089363.14, https://www.ncbi.nlm.nih.gov/clinvar/, last accessed May 15, 2021), confirming the diagnosis of CMMRD (Fig. 2A). Genetic testing showed that the patient’s mother and father were heterozygous carriers of the MSH6 c.3261del mutation, leading to the diagnosis of Lynch syndrome based on the same germline mutation in both parents (Fig. 3A, B). Both parents had normal findings by colonoscopy and esophagoduodenoscopy.

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**Fig. 1** Findings of computed tomography scan, physical examination, and CMMRD scoring system. A Abdominal computed tomography image showing rectal wall thickening without lymphadenopathy (white arrowheads). B, C On physical examination, several café au lait macules and multiple cutaneous hemangiomas on back and right leg, respectively, are visible. D The patient had scores of 5 and 14 points, before and after genetic testing, respectively, according to the CMMRD scoring system. ■ criteria fulfilled before genetic testing; ◆ criteria fulfilled after genetic testing; □ unfilled criteria; CMMRD, constitutional mismatch repair deficiency.
**Fig. 1** (See legend on previous page.)

### CMMRD scoring system for a clinical suspicion of CMMRD in cancer patients

| Indication for CMMRD testing in cancer patients | 3 points or more |
|-----------------------------------------------|------------------|
| Malignancies/premalignancies: one is mandatory; if more than one is present in the patient, add the points |                  |
| ◆ Carcinoma from the LS spectrum at age <25 years | 3                |
| ◆ Multiple bowel adenomas at age <25 years and absence of APC/MUTYH mutation(s) or a single high-grade dysplasia adenoma at age <25 years | 3                |
| □ WHO grade III or IV glioma at age <25 years | 2                |
| □ NHL of T-cell lineage or sPNET at age <18 years | 2                |
| □ Any malignancy at age <18 years | 1                |
| Additional features: optional; if more than one of the following is present, add the points |                  |
| ■ Clinical sign of NF1 and/or 2 hyperpigmented and/or hypopigmented skin alterations >1 cm in the patient | 2                |
| ■ Diagnosis of LS in a first-degree or second-degree relative | 2                |
| ■ Carcinoma from LS spectrum before the age of 60 in first-degree, second-degree, or third-degree relative | 1                |
| □ A sibling with carcinoma from the LS spectruma, high-grade glioma, sPNET, or NHL | 2                |
| □ A sibling with any type of childhood malignancy | 1                |
| □ Multiple pilomatricomas in the patient | 2                |
| □ One pilomatricoma in the patient | 1                |
| □ Agenesis of the corpus callosum or non-therapy–induced cavernoma in the patient | 1                |
| □ Consanguineous parents | 1                |
| ■ Deficiency/reduced levels of IgG2/4 and/or IgA | 1                |

CMMRD, constitutional mismatch repair-deficiency; LS, Lynch syndrome; WHO, World Health Organization; sPNET, supratentorial primitive neuroectodermal tumors; NHL, Non-Hodgkin’s lymphoma
Fig. 2  Colonoscopic and pathological findings of colorectal polyps. A, B Colonoscopy showing a sessile polyp with a central depression in the rectosigmoid area and multiple polyps. C Gross image of the resected rectosigmoid colon. A total of 13 polyps, with maximum diameters of up to 45 mm, are found. D Microscopic view of the largest polyp (white arrowhead in B). Intramucosal adenocarcinoma (pT1) with complex cribriform architecture in adenoma. E, F Microscopic view of other polyps (black and white arrows in C). Low-grade tubular adenoma.
During the first colonoscopy after surgery, two polyps were pathologically diagnosed as intramucosal adenocarcinoma (pTis) in adenoma. However, in the third colonoscopy, one polyp, sized 8 mm, in descending colon was diagnosed as invasive adenocarcinoma without lymphovascular invasion (>1000 μm, pT1). The patient refused the recommended additional surgery including colectomy. Subsequently, surveillance endoscopy and CT examination were continued, and lymph node and distant metastases were not present at last follow-up at three years after initial surgery. During the 3-year follow-up period with short-interval surveillance colonoscopy, 130 colon polyps were removed without adverse events, and the number of detected polyps gradually decreased (Table 1). The duodenal adenoma was treated with endoscopic mucosal resection after LAR. Until the last follow-up, the subsequently performed annual esophagoduodenoscopy and capsule endoscopy led to the identification of three duodenal adenomas, sized <5 mm, which were removed.

**Discussion and conclusions**

Recent studies suggest that >50%, 40%, and 30% of patients with CMMRD develop malignant brain tumors, gastrointestinal tumors, and hematological malignancies, all during childhood, reflecting the generally poor prognosis of CMMRD [4]. The most frequent CMMRD-associated cancers are brain glioma diagnosed at 9.5 years of age, non-Hodgkin’s lymphoma diagnosed at 5 years of age, and colorectal cancer diagnosed at 16 years of age [11]. Besides very high tumor risks, CMMRD phenotypes are often characterized by the presence of signs reminiscent of neurofibromatosis type 1 [8]. The present 13-year-old patient with CMMRD and history of T-lymphoblastic lymphoma is a case of colon polyposis caused by biallelic germline mutation in an MMR gene.

The management of colon cancer in patients with CMMRD is based on the frequency of synchronous or metachronous gastrointestinal and non-gastrointestinal cancers. The International BMMRD Consortium reported that the approximate frequencies of synchronous and metachronous colorectal cancers were 20 and 50%, respectively [7]. Therefore, an aggressive approach, including colectomy with ileorectal anastomosis or proctocolectomy and construction of an ileal pouch-anal anastomosis, is recommended for colon polyposis in CMMRD patients [5]. Moreover, close monitoring of the rectum with endoscopy every 6 or 12 months is crucial after ileorectal anastomosis. However, metachronous non-colorectal cancers are frequent in patients with CMMRD [12]. Among eight patients with CMMRD and colorectal cancer, small intestinal and non-gastrointestinal cancers were diagnosed after the treatment of colorectal cancer in one and three patients, respectively [7]. Moreover, the cancer spectrum is reported to be related to specific MMR gene mutations. MSH6 and/or PMS2 mutations lead to cancers within ten years of life, and 34% of patients with MSH6 mutations develop a second metachronous malignancy. The current patient and his parents refused colectomy after considering the high risk of metachronous cancers including non-gastrointestinal cancers.

In the present patient, the treatment strategy for colon polyposis was based on the endoscopic treatment for familial adenomatous polyposis (FAP), in which colectomy is a standard approach to prevent colorectal cancer [13]. However, colectomy is also associated with morbidity and mortality and removal of the large intestine affects quality of life [14, 15]. Therefore, the efficacy and safety of endoscopic management for colon clearance was considered in the current patient. In a study of patients with FAP refusing surgery, invasive colorectal cancer was not observed during a median follow-up of 5.1 years and there were no complications, suggesting that endoscopic management might prevent cancer development in patients with FAP [10, 16]. On the other hand, partial colectomy with subsequent regular surveillance colonoscopy is recommended in patients with Lynch syndrome and colorectal cancer, although the appropriate interval of surveillance colonoscopy after partial colectomy remains unclear [17]. However, colonoscopy performed in 6-month intervals was occasionally insufficient to detect endoscopically resectable tumors in some patients with high risk Lynch syndrome. Indeed, the present patient was diagnosed with an invasive cancer in descending colon during third colonoscopy after LAR. Additional surgery should be done in cases of endoscopically resected T1 cancer with positive vertical margin, although the relapse ratio of approximately 3.4% is relatively low [18]. Therefore, our strategy should be considered when colectomy is not appropriate due to patient’s condition.
Fig. 3 (See legend on previous page.)

A

I

II

III

IV

E+(c.3261delC MSH6)

E+(c.3261delC MSH6)

E+(c.3261delC MSH6 homozygosis)

Colorectal cancer over 50 years old

T lymphoblastic lymphoma and colorectal cancer

B

**MSH6 Exon5**

| 1084 | 1085 | 1086 | 1087 | 1088 | 1089 | 1090 | 1091 | 1092 |
|------|------|------|------|------|------|------|------|------|
| Asp  | Thr  | Pro  | Pro  | Phe  | Leu  | Glu  | Leu  | Lys  |

Control

Father

Patient

Mother
Recent studies analyzing the association between tumor genetics and clinical spectrum should lead to the development of appropriate treatment strategies in patients with CMMRD [19]. In a study utilizing next-generation sequencing of 17 high-grade brain tumors in patients with CMMRD, the tumors exhibited massive numbers of substitution mutations (average, 7911 coding mutations; 249 mutations/Mb), which were higher than that observed in tumors of patients without CMMRD (0.61 mutations/Mb); the CMMRD-associated tumors were termed ultra-hypermutated cancers [20]. Moreover, these cancers acquired driver mutations in DNA polymerase ε (POLE) or δ (POLD1), which appeared to result in the loss of replication fidelity and a high mutation rate [21]. Gastrointestinal polyps without POLE and POLD1 mutations in patients with CMMRD did not exhibit higher mutational loads. Another study reported differences in the prevalence rates of hematological, brain, and Lynch syndrome-associated cancers among patients with CMMRD harboring MLH1/MSH2, MSH6, and PMS2 mutations5. These results should contribute to the adjustment of treatment modalities, offering surveillance strategies for second malignancies and appropriate counseling of the entire family.

In the present patient with CMMRD and colon polyposis, intensive surveillance endoscopy for multiple gastrointestinal tumors enabled the reduction in the number of lesions. The standard of care should be colectomy or proctocolectomy for colorectal polyposis in patients with CMMRD. However, our experience of short surveillance endoscopy illustrates that our strategy might be one of options according to patient’s condition.

**Abbreviations**
CMMRD: Constitutional mismatch repair deficiency; CT: Computed tomography; LAR: Low anterior resection; FAP: Familial adenomatous polyposis.

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**Table 1** Clinicopathological characteristics of colon polyps treated during surveillance colonoscopy after surgery

| Session after surgery | Total number of colon polyps removed | Carcinoma diagnosis | Carcinoma characteristics |
|-----------------------|-------------------------------------|---------------------|--------------------------|
|                       |                                     |                     | Location | Growth type | Size (mm) | pT stage* | Horizontal margin | Vertical margin |
| 1                     | 2                                  | Yes                 | S        | Polypoid     | 20        | pTis      | (−)                 | (−)             |
| 2                     | 7                                  | No                  | R        | Polypoid     | 17        | pTis      | (−)                 | (−)             |
| 3                     | 12                                 | Yes                 | D        | LST-NG       | 8         | pT1       | (ND)                | (ND)            |
| 4                     | 18                                 | No                  |          |              |           |          |                     |                 |
| 5                     | 24                                 | No                  |          |              |           |          |                     |                 |
| 6                     | 30                                 | No                  |          |              |           |          |                     |                 |

*Based on classification system by the Union for International Cancer Control

S sigmoid colon, R rectum, D descending colon, LST-NG laterally spreading tumor non-granular type, ND not determined

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**Authors’ contributions**
TA, RF, KN, MS, IM, HM, SN, SK, HF, SH managed the patient and family and performed surveillance endoscopy. TN evaluated histology of resected specimens. YN performed mutational analysis. TA, YN, TF and IY wrote and edited the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**
The datasets used and/or analyzed during this study are included in this paper and shall be available from the corresponding author upon request.

**Declarations**

**Ethics approval and consent to participate**
This study was approved by the medical ethics committee of the Toyama University Hospital (E2021001).

**Consent for publication**
Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

**Competing interests**
The authors declare that they have no competing interests.

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