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ABOUT COVER

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AIMS AND SCOPE

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CASE REPORT

MutL homolog 1 germline mutation c.(453+1_454-1)_(545+1_546-1)del identified in lynch syndrome: A case report and review of literature

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Abstract

BACKGROUND

Lynch syndrome (LS) is an autosomal dominant hereditary disorder because of germline mutations in DNA mismatch repair genes, such as MutL homolog 1 (*MLH1*), PMS1 homolog 2, MutS homolog 2, and MutS homolog 6. Gene mutations could make individuals and their families more susceptible to experiencing various malignant tumors. In Chinese, *MLH1* germline mutation c.(453+1_454-1)_(545+1_546-1)del-related LS has been infrequently reported. Therefore, we report a rare LS patient with colorectal and endometrioid adenocarcinoma and describe her pedigree characteristics.

CASE SUMMARY

A 57-year-old female patient complained of irregular postmenopausal vaginal bleeding for 6 mo. She was diagnosed with LS, colonic malignancy, endometrioid adenocarcinoma, secondary fallopian tube malignancy, and intermyometrial leiomyomas. Then, she was treated by abdominal hysterectomy, bilateral oviduct oophorectomy, and sentinel lymph node resection. Genetic testing was performed using next-generation sequencing technology to detect the causative genetic mutations. Moreover, all her family members were offered a free genetic test, but no one accepted it.

CONCLUSION

No tumor relapse or metastasis was found in the patient during the 30-mo follow-up period. The genetic panel sequencing showed a novel pathogenic germline mutation in *MLH1*, c.(453+1_454-1)_(545+1_546-1)del, for LS. Moreover, cancer genetic counseling and testing are still in the initial development state in China, and maybe face numerous challenges in the further.

Key Words: Lynch syndrome; Colorectal cancer; Endometrial cancer; *MLH1* gene; Gene testing; Case report

Core Tip: Lynch syndrome (LS) is an autosomal dominant hereditary disorder because of germline mutations in DNA mismatch repair genes, such as MutL homolog 1 (*MLH1*) gene, PMS1 homolog 2 gene, MutS homolog 2 gene, and MutS homolog 6 gene, which make the patient more susceptible to other malignancies. In Chinese, *MLH1* germline mutation c.(453+1_454-1)_(545+1_546-1)del-induced LS has been infrequently reported. In this paper, we report a rare LS patient with colorectal and endometrioid adenocarcinoma. The genetic panel sequencing showed a novel pathogenic germline mutation in *MLH1*, c.(453+1_454-1)_(545+1_546-1)del, for LS.

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INTRODUCTION

Lynch syndrome (LS) is an autosomal dominant inherited disorder because of germline mutations in DNA mismatch repair (*MMR*) genes, such as MutL homolog 1 (*MLH1*), PMS1 homolog 2 (*PMS2*), MutS homolog 2 (*MSH2*), and MutS homolog 6 (*MSH6*), which make the patient more susceptible to other malignancies[1,2]. *MLH1*, *MSH2*, *MSH6*, and *PMS2* mutations in LS account for approximately 50%[3-5], 40%[5], 7%-20%[3-8], and < 6%[3,4,9] of all cases, respectively. Additionally, specific *MMR* gene deficiencies might result in different ages of onset, types of malignancy, and clinical signs[10]. The *MLH1* gene defects could decrease the expression of *MLH1* protein, affecting the MMR function, leading to errors in DNA replication and ultimately inducing neoplams[11,12].

LS can be classified as types I and II according to the location of tumors[3,13,14]. Type I is an intestinal neoplasm, such as colorectal cancer[14]. Besides, type II is defined as colorectal malignancy complicated with parenteral cancers, including gastric cancer[15], renal cell cancer[16], epithelial ovarian cancer[17], endometrial cancer[2], bladder cancer[18,19], breast cancer[20], and even repeated stroke[10]. Endometrial cancer is the most frequent parenteral tumor among LS patients[21,22], which ranks 3rd in the mortality of all gynecological cancers[23]. In recent years, LS-associated endometrial cancer (LSAEC) has received increasing attention in the medical field[24]. Furthermore, the offspring of LS patients will have a 50% incidence of inheritance[24]. More than 2600 mutations have been reported worldwide[10,24,25], but *MLH1* exon 6 c.(453+1_454-1)_(545+1_546-1)del-induced LS has been rarely described in Chinese. Therefore, we present a rare case with an *MLH1* germline mutation, analyze her pedigree characteristics, and review the *MLH1* gene mutation loci.

CASE PRESENTATION

Chief complaints

A 57-year-old Chinese female patient complained of irregular postmenopausal vaginal bleeding. The demographic characteristics of the patient are listed in Table 1.

History of present illness

The patient had the clinical symptom of irregular vaginal bleeding for 6 mo.

History of past illness

The patient had a medical history of colon cancer and received a radical colon cancer operation 20 years ago.

Personal and family history

The patient and many of her family members had a cancer history.

Table 1 Demographic characteristics

Parameter	Outcome
Sex	Female
Age (yr)	57
Sample type	Peripheral venous blood
Genes	*EPCAM, MLH1, MSH2, MSH6, PMS2, STK11, TP53, PTEN, MUTYH, BRCA1, MLH3*
Length of the target region (bp)	49287
Target area coverage	100%
Average depth of target area (×)	608.777386
Average depth of target area > 30 × the proportion of sites	99.78%
Detection range	Exon and its adjacent ± 20 bp intron region

EPCAM: Epithelial cell adhesion molecule; *MLH1*: MutL homolog 1; *MSH2*: MutS homolog 2; *MSH6*: MutS homolog 6; *PMS2*: PMS1 homolog 2; *STK11*: Serine-Threonine Kinase 11; *TP53*: tumor protein 53; *PTEN*: Phosphatase and tensin homolog; *MUTYH*: Mut Y homolog; *BRCA1*: Breast cancer gene 1; *MLH3*: MutL homolog 3.

Physical examination

A small amount of white secretions with no odor was found in the vagina. A smooth cervical surface was detected. The vulva was atrophic, the vagina was patent, and mucosal fold atrophy was palpated. Moreover, the uterine was in an anterior position, with a smooth surface and good range of motion. No obvious abnormality was found in the bilateral adnexal areas.

Laboratory examinations

No abnormality was found in the routine blood tests.

Imaging examinations

Ultrasound

Preoperative abdominal Doppler ultrasound showed that the uterus, with a size of 3.8 cm × 3.5 cm × 3.1 cm, was located in an anterior position, the uterine cavity line was clear, the endometrial thickness was 1.1 cm (significantly greater than the normal value of endometrial thickness in postmenopausal women), and the ultrasonic echo of the endometrium was uneven. In addition, bilateral ovaries and adnexa presented no abnormality. Color Doppler flow imaging showed no abnormal blood flow signal.

Magnetic resonance imaging

Abdominal magnetic resonance imaging showed that the uterus was in an anteversion and flexion position. A mass with an equal T1 and slightly long T2 signal was found in the uterine cavity, with an unclear boundary (Figure 1A). The tumor size was about 31 mm × 23 mm, and the display of the uterine junction was not clear (Figure 1B and C). The enhanced images showed that the lesions exhibited inhomogeneous enhancement. Diffusion-weighted imaging showed that the lesions exhibited a high signal. The shape and signal of the bilateral adnexa were normal (Figure 1D). There was no obvious abnormal signal in the bladder and rectum. No abnormality was found in bilateral iliac vessels and inguinal lymph nodes. No effusion was found in the pelvic cavity, and no obvious abnormal signal was found in pelvic wall soft tissue.

FINAL DIAGNOSIS

The clinical diagnosis was endometrioid adenocarcinoma (IIIA1) and LS.

TREATMENT

After general anesthesia, abdominal hysterectomy and bilateral oviduct oophorectomy were performed. The whole uterus and bilateral appendages were examined during the operation by fast-frozen histopathology. It revealed a poorly differentiated adenocarcinoma of the uterus, which infiltrated the

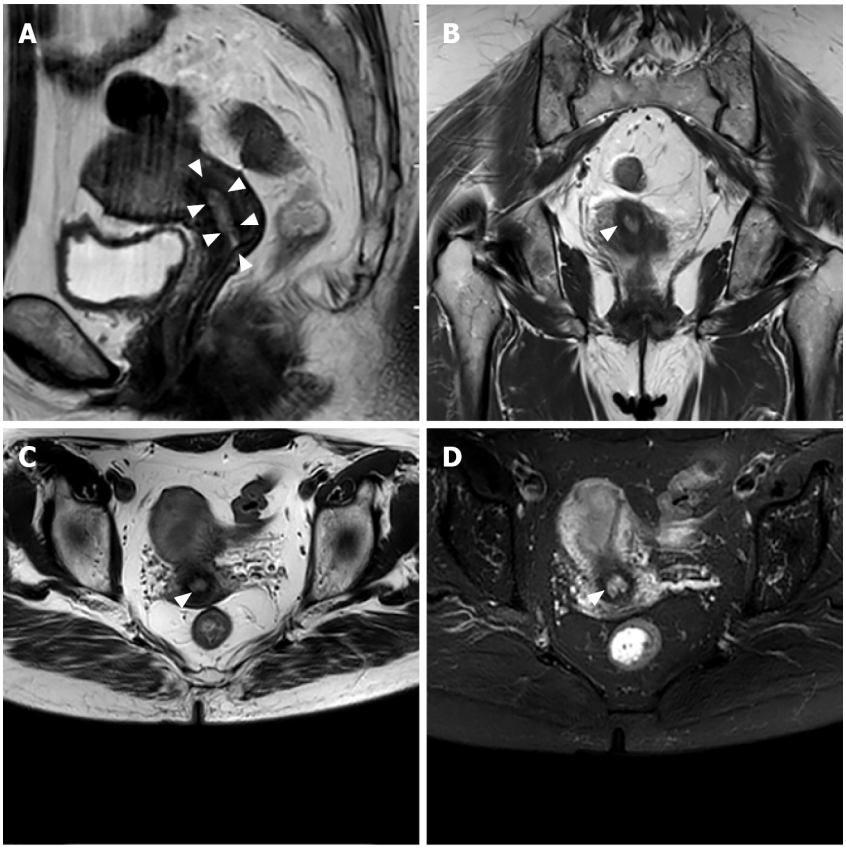

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Figure 1 Preoperative abdominal magnetic resonance imaging. A: Sagittal magnetic resonance imaging (MRI) showed an equal T1 and slightly longer T2 signal in the uterine cavity; B: Coronal MRI image; C: Axial MRI image. D: Enhanced MRI image showing that the lesions were inhomogeneous enhanced. The white arrowheads represent lesions. The tumor size was approximately 31 mm × 23 mm (B and C).

superficial muscularis. Subsequently, sentinel lymph node resection was also performed. After surgery, the patient was treated with regular chemotherapy for six courses, including paclitaxel (Nanjing Green Leaf Pharmaceutical Co., Ltd., Nanjing, China) and carboplatin injection (Qilu Pharmaceutical Co., Ltd., Jinan, China).

OUTCOME AND FOLLOW-UP

The biopsy histochemical (hematoxylin-eosin) staining showed that endometrial cancer was moderately to poorly differentiated. A few of its lesions were accompanied by squamous differentiation. The tumor infiltrated into the superficial muscle wall. Noticeably, one side of the fallopian tube showed cancerous lesions, while the other side of the fallopian tube and bilateral ovaries showed no cancerous lesions. However, cervical vessels, blood vessels, lymphatic vessels, and nerves were not invaded. Bilateral pelvic lymph nodes were normal.

Immunohistochemical (IHC) staining results showed MLH1 (-), PMS2 (-), MSH6 (+-), MSH2 (+-), BRAF V600E mutation-specific antibody (VE1) (Ventana IHC enhanced amplification kit) (-), CD31 (-), D2-40 (-), CK5/6 (partial lesions +-), p63 (+-), and CDX2 (-) (Figure 2). Besides, the positive rate of PR was 90+ACU- (+-). The positive rate of ER was 90+ACU- (+-). The positive rate of Ki67 was 60+ACU-. P53 was scattered weak positive, and P16 was partially positive. Based on these findings, the patient was diagnosed with endometrioid adenocarcinoma (IIIA1).

No tumor recurrence or metastasis was found during a 2.5-year follow-up period. Computed tomography was performed after six chemotherapy courses and showed no abnormality in the head, liver, gallbladder, spleen, pancreas, bilateral kidney, bilateral ureter, rectum, or lung.

The results of gene sequencing are shown in Tables 2 and 3. A heterozygous deletion mutation of exon 6 was detected in the *MLH1* gene, which was named c.(453+-1+AF8-454-1)+AF8-(545+-1+AF8-546-1)del according to the Human Genome Variation Society (Figure 3). Postoperatively, the patient was diagnosed with LS, endometrioid adenocarcinoma (IIIA1), colonic malignancy, secondary fallopian tube malignancy, and intermyometrial leiomyomas.

Table 2 Gene detection of hereditary endometrial cancer

Parameter	Outcome
Diagnosis	Hereditary EC
Gene (NM number)	*MLH1* (NM_000249.3)
Nucleotide changes	Exon 6 del
Amino acid changes	-
Gene subregion	Exon 6
Heterozygous	Heterozygous mutation
Functional changes	Deletion
Genetic model	AD
Gene mutation type	Known pathogenic mutation

EC: Endometrial cancer; AD: Autosomal dominant inheritance; *MLH1*: MutL homolog 1.

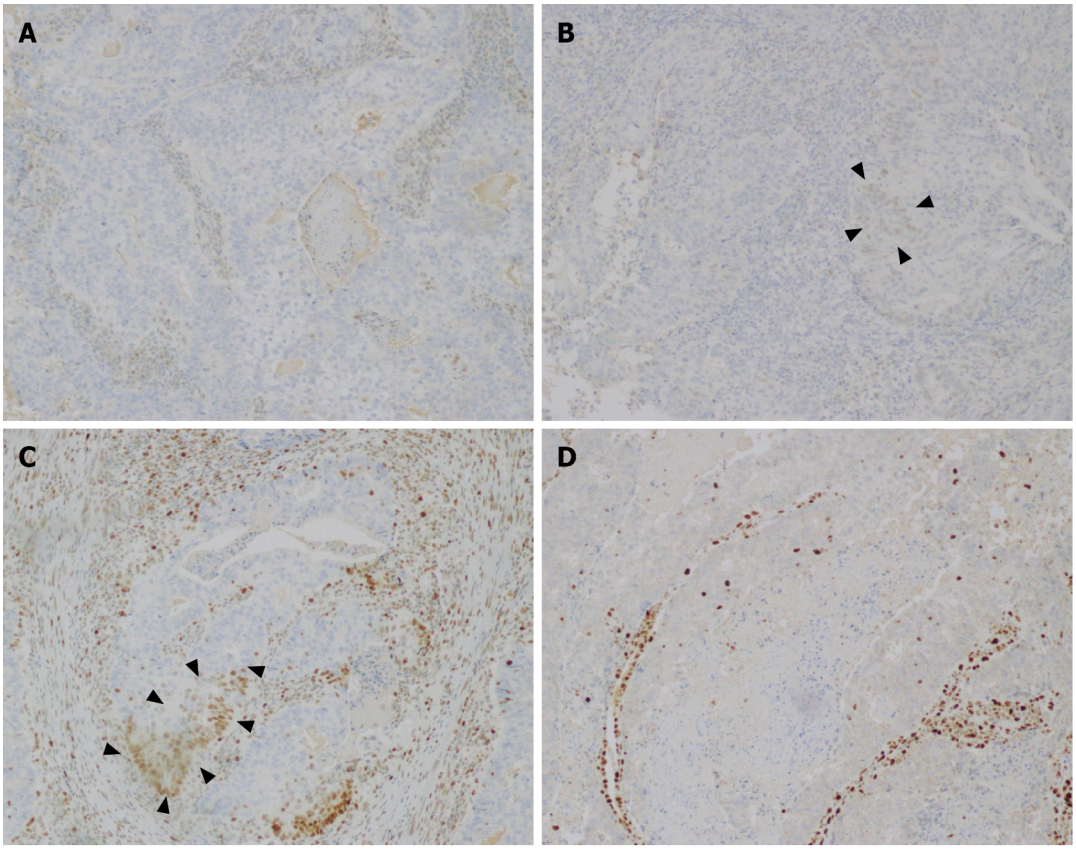

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Figure 2 Immunohistochemical images. A: Loss of MLH1 proteins was found in the tumor cells; B: Expression of MSH2 protein was detected in the tumor cells; C: Expression of MSH6 protein was detected in the tumor cells; D: Loss of PMS2 protein was found in the tumor cells.

The patient's eldest sister was diagnosed with colon cancer at age 60, the second sister with endometrial cancer at age 60, the third sister with colon cancer at age 40, the older brother with colon polyps three times between the ages of 40 and 50, the mother with endometrial cancer at age 48, and the mother with colon cancer at age 50. The prevalence spectrum of the four generations of patients is shown in Figure 4.

Genetic counseling was conducted among the family relatives. Moreover, we provided free Sanger mutation site verification tests for the family members of the patient. However, all relatives refused to be tested.

Table 3 Variation information of exon region and its adjacent ± 20 bp intron region in hereditary endometrial cancer

No.	Gene	Transcript	NV	AAC	GS	Heterozygous	Rs NO.	FC	MT
1	*MLH1*	NM_000249.3	EX6 DEL	-	EX6	Het	-	Deletion	Kv
2	*MLH1*	NM_000249.3	c.1151T>A	p.Val384Asp	CDS12	Het	rs63750447	Missense	Bp
3	*MUTYH*	NM_001128425.1	c.74G>A	p.Gly25Asp	CDS2	Het	rs75321043	Missense	Uv
4	*MUTYH*	NM_001128425.1	c.53C>T	p.Pro18Leu	CDS2	Het	rs79777494	Missense	Uv
5	*MUTYH*	NM_001128425.1	c.36+11C>T	-	IN1	Het	rs2275602	Splice	Bp
6	*MUTYH*	NM_001128425.1	c.1014G>C	p.Gln338His	CDS12	Het	rs3219489	Missense	Bp
7	*BRCA1*	NM_007294.3	c.2612C>T	p.Pro871Leu	CDS9	Het	rs799917	Missense	Bp
8	*BRCA1*	NM_007294.3	c.4837A>G	p.Ser1613Gly	CDS14	Het	rs1799966	Missense	Bp
9	*BRCA1*	NM_007294.3	c.3548A>G	p.Lys1183Arg	CDS9	Het	rs16942	Missense	Bp
10	*BRCA1*	NM_007294.3	c.3113A>G	p.Glu1038Gly	CDS9	Het	rs16941	Missense	Bp
11	*EPCAM*	NM_002354.2	c.344T>C	p.Met115Thr	CDS3	Het	rs1126497	Missense	Bp
12	*MLH3*	NM_014381.2	c.2531C>T	p.Pro844Leu	CDS1	Het	rs175080	Missense	Bp
13	*MLH3*	NM_014381.2	c.2476A>G	p.Asn826Asp	CDS1	Hom	rs175081	Missense	Bp
14	*MSH2*	NM_000251.2	c.211+9C>G	-	IN1	Het	rs2303426	Splice	Bp
15	*MSH6*	NM_000179.2	c.3438+14A>C	-	IN5	Hom	rs2020911	Splice	Bp
16	*PMS2*	NM_000535.6	c.1408C>T	p.Pro470Ser	CDS11	Het	rs1805321	Missense	Bp
17	*PMS2*	NM_000535.6	c.2570G>C	p.Gly857Ala	CDS15	Hom	rs1802683	Missense	Bp
18	*PMS2*	NM_000535.6	c.706-4delT	-	IN6	Het	rs6079473	Splice	Bp
19	*PMS2*	NM_000535.6	c.59G>A	p.Arg20Gln	CDS2	Het	rs10254120	Missense	Bp
20	*PMS2*	NM_000535.6	c.1621A>G	p.Lys541Glu	CDS11	Hom	rs2228006	Missense	Bp
21	*PMS2*	NM_000535.6	c.705+17A>G	-	IN6	Het	rs62456182	Splice	Bp
22	*PMS2*	NM_000535.6	c.2007-4G>A	-	IN11	Het	rs1805326	Splice	Bp
23	*PMS2*	NM_000535.6	c.2007-7C>T	-	IN11	Het	rs55954143	Splice	Bp
24	*PTEN*	NM_000314.6	c.802-3dupT	-	IN7	Het	rs762344516	Splice	Bp
25	*TP53*	NM_000546.5	c.215C>G	p.Pro72Arg	CDS3	Het	rs1042522	Missense	Bp

EC: Endometrial cancer; NV: Nucleotide variation; AAC: Amino acid changes; GS: Gene subregion; Rs NO.: rs number; FC: Functional changes; MT: Mutation types; Kv: Known variation; Uv: Unknown variation; Bp: Benign polymorphism; Het: Heterozygous; Hom: Homozygous.

DISCUSSION

Colorectal cancer is the 5th commonly diagnosed cancer in China[23,26]. In 2015, the number of colorectal cancer-related deaths and new cases in China was approximately 191000 and 376300, respectively. Moreover, hereditary colorectal malignancy accounts for 5%-10% of colorectal malignancies, including LS, Li-Fraumeni syndrome, MUTYH-associated polyposis, juvenile polyposis syndrome, familial adenomatous polyposis, and Peutz-Jeghers syndrome[27]. In this study, the patient had a medical history of colon cancer 20 years ago and has experienced endometrial adenocarcinoma. We found that the patient carries a novel pathogenic genetic deletion mutation in *MLH1*. Many researchers have reported diseases caused by *MLH1* gene mutations[28-31]. Hong *et al*[31] detected that the deletion of exon 7 to exon 19 of the *MLH1* gene was a pathogenic mutation causing colorectal cancer. Jia *et al*[28] reported that the p.K618del variant in *MLH1* was the causative pathogenic genetic variant for LS. Solassol *et al*[29] found that an *AluY5a* insertion in *MLH1* exon 6 led to exon skipping, which resulted in a pathogenic frameshift in patients who developed colorectal adenocarcinomas. Li *et al*[30] reported that the insertion of a truncated *AluSx* like element into *MLH1* intron 7 resulted in aberrant splicing and transcription, thus inducing LS. Lagerstedt-Robinson *et al*[32] reported an LS patient with the deletion of *MLH1* c.(453+1_454-1)_(545+1_546-1) in Switzerland. However, in China, the *MLH1*genetic mutation c.(453+1_454-1)_(545+1_546-1) del has not been reported. Consequently, we present a relatively rare LS patient with *MLH1* c.(453+1_454-1)_(545+1_546-1)del and describe the clinical features, pathological features, and familial morbidity of the proband.

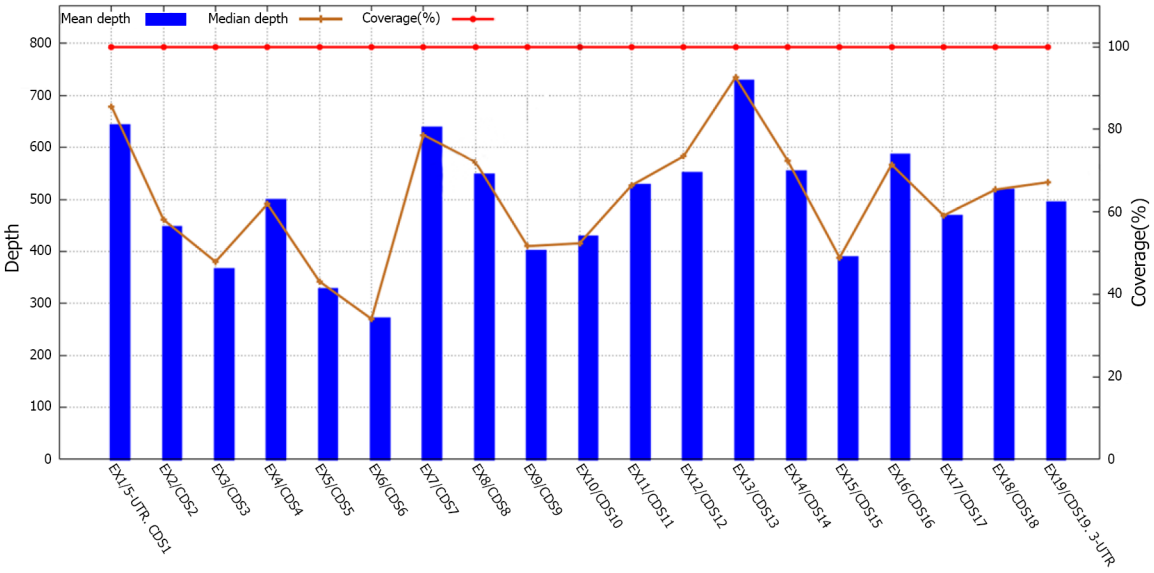

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Figure 3 Figures related to gene test results. A deletion mutation of exon 6 was found in the *MLH1* gene.

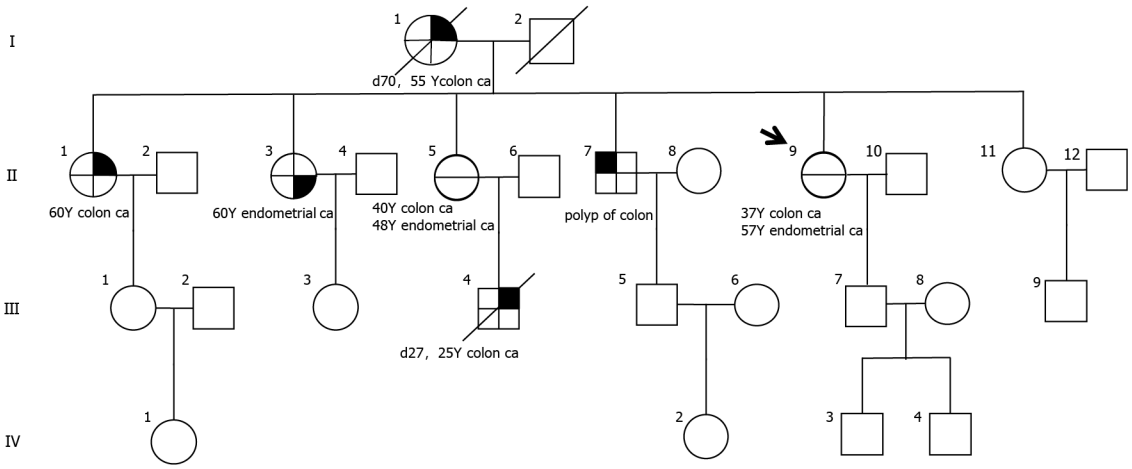

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Figure 4 Family pedigree. The reconstructed pedigree demonstrates that the proband (II-9), her mother (I-1), her sisters (II-1, II-3, and II-5) and her brother (II-7), and her sister's son (IV-4) experienced cancer. I-1 was diagnosed with colon cancer at 55 years and died at 70 years. II-1 and II-3, both at 60 years, suffered from colon cancer and endometrial cancer, respectively. II-5 experienced colon cancer at 40 years and endometrial cancer at 48 years. II-7 developed polyps of the colon at unknown age. III-4 had colon cancer at 25 years and died at 27 years. The arrow indicates the proband. Solid symbols reveal persons affected by malignancy. The symbol with a slash indicates a deceased individual with age at death. Circles indicate female family members, and squares suggest male family members.

The demographic characteristics of LSAEC are as follows: First, the pathological types are diverse and poorly differentiated. Second, the onset age is between 46 and 54 years old. Third, the majority of the pathological changes are situated in the lower segment of the corpus uteri[33]. The potential risk of LS patients experiencing another cancer at 10 and 15 years was 25% and 50%, respectively[34]. The present case had colon cancer at age 37. Twenty years later, she was diagnosed with endometrioid adenocarcinoma. The demographic characteristics of the present patient were similar to those reported in the previous studies[21,34].

Concerning the diagnosis of LS, Amsterdam II[35] and Bethesda[36] criteria have been widely used to screen for LS. In the present study, the patient met the criteria of the Amsterdam standard II and the revision of the Bethesda guidelines. Nonetheless, the two standards' sensitivity is low because they are based on clinical background and family history[37-39]. Thus, Amsterdam II and Bethesda criteria are inadequate as independent screening tools.

IHC was a useful method for LS screening[37,40,41], particularly in colorectal malignancy patients. The sensitivity and specificity of IHC in patients with MMR mutations are 83% and 89%, respectively [42]. When IHC results suggest deleting *MLH1* and *PMS2* proteins, universal screening including *BRAF* testing and *MLH1* promoter methylation analysis is required[10,22,24,25,28,38-40,43,44]. In the present

study, the IHC results showed the loss of *MLH1* and *PMS2* proteins, but expression of *MSH2* and *MSH6* proteins in the tumor cells. Subsequently, *MLH1* mutation was considered. The patient had a medical history of colon cancer and a family history of LS-related cancers. Then, she was diagnosed with LS. Also, we advised the patient and her family members to receive genetic counseling.

Before genetic testing, we provided genetic counseling for the patient and obtained a clear LS family history. We found that the proband's mother (I-1) suffered from primary colon cancer at 55 years and died at 70 years, two of her sisters [(II-1) and (II-3)] were affected by colon cancer at 60 years and endometrial cancer at 60 years, respectively, one of her sisters (II-5) experienced colon cancer at 40 years and endometrial cancer at 48 years, her brother (II-7) developed polyps of the colon, and her nephew developed colon cancer at 25 years and died at 27 years. Besides, standard processes of cancer-related genetic counseling should include pre-test counseling, results analysis, and follow-up[28]. In our study, the family history suggested the clinical diagnosis of LS. Then, the patient and family members were given detailed pre-test counseling. However, we cannot make a definitive diagnosis of LS without genetic testing[28]. Consequently, genetic testing was recommended for the proband and her relatives.

Furthermore, we provided free genetic tests for all her family members to help at-risk offspring know their risk of developing cancers, thus enabling them to access personalized precision medicine. Unexpectedly, only the proband received the genetic test, but her family members refused. The reasons for the relatives of the proband to refuse genetic testing are as follows: First, they were worried that their genetic problems may cause difficulties in mate selection or affect the stability of marriage. Second, they will be unable to purchase life insurance if they have a genetic defect. Third, they are worried about personal privacy exposure. Wang *et al*[45] investigated the willingness and awareness of genetic screening for patients undergoing colon cancer surgery at Peking Union Medical College Hospital who had any protein (*MLH1/MLH2/MLH6/PMS2*) expression deletion suggested by IHC, and the result indicated that 27.4% (61/219) of the patients explicitly refused to undergo genetic screening. The findings of our study and Wang *et al*[45] indicate that gynecologists should strengthen health education. Therefore, cancer genetic counseling and testing are still in the initial development stage in China, and maybe face numerous challenges in the further[28]. This dilemma is expected to be improved with better preventative education to the general population and a better understanding of cancer genetics among cancer patients and medical practitioners[28].

The patient achieved positive clinical outcomes during the 30-mo follow-up visit period. However, several limitations exist in this study. First, 6 mo after discharge, the proband's 25-year-old offspring (III-4) was diagnosed with colon cancer and died at age 27. We believe that this unfortunate outcome could have been prevented if her family members had taken genetic testing and then received individualized preventive treatment before the malignant tumor onset. Thus, it is essential to enhance genetic testing awareness among the Chinese population, especially in rural areas.

CONCLUSION

MLH1 exon 6 c.(453+1_454-1)_(545+1_546-1)del mutation is a novel pathogenic mutation of LS in Chinese. This case report emphasizes the value of diagnosis and treatment in patients with inherited malignancy syndromes. To date, cancer genetic counseling and testing are still in the initial development state in China, and maybe face numerous challenges in the further.

FOOTNOTES

Author contributions: Zhang XW, Jia ZH, and Zhao LP were the patient's gynecologic surgeons, reviewed the literature, and contributed to manuscript drafting; Wu YS, Xu TM, and Jia Y were responsible for the revision of the manuscript for important intellectual content; Cui MH analyzed and interpreted the imaging findings; all authors issued final approval for the version to be submitted.

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