Case Reports in Oncology

Case Rep Oncol 2023;16:628–633
DOI: 10.1159/000531837
Received: March 6, 2023
Accepted: June 21, 2023
Published online: August 16, 2023

Case Report

Endometrial Cancer Diagnosed at an Early Stage during Lynch Syndrome Surveillance: A Case Report

Maki Umemiya[a] Naoki Horikawa[a] Ami Kanai[a] Ayaka Saeki[a] Kohei Ida[a] Satoru Makio[a] Teruki Yoshida[a] Mitsuru Tsuji[a] Rei Gou[a] Hirohiko Tani[a] Takeshi Usui[b, c] Kenzo Kosaka[a]

[a]Department of Obstetrics and Gynecology, Shizuoka General Hospital, Shizuoka, Japan; [b]Department of Genetics, Shizuoka General Hospital, Shizuoka, Japan; [c]Shizuoka Graduate University of Public Health, Shizuoka, Japan

Keywords
Lynch syndrome · Endometrial cancer · Gynecologic cancer surveillance · Cancer panel testing

Abstract
Lynch syndrome is an autosomal dominant inherited disorder caused by a germline pathogenic variant in DNA mismatch repair genes, resulting in multi-organ cancer. Annual transvaginal ultrasonography and endometrial biopsy are recommended for endometrial cancer surveillance in patients with Lynch syndrome in several guidelines; however, evidence is limited. Here, we present the case of a 51-year-old woman with endometrial cancer who underwent robot-assisted laparoscopic simple hysterectomy at an early stage detected by Lynch syndrome surveillance. The patient was a 51-year-old gravida zero woman without any medical history or symptoms. Her sister suffered from bladder, breast, rectal, and endometrial cancer and was diagnosed with Lynch syndrome using a hereditary cancer panel test (VistaSeq®). During gynecologic surveillance, the patient's endometrial cytology was classified as Papanicolaou class III. Therefore, she underwent endometrial curettage with hysteroscopy and was diagnosed with atypical endometrial hyperplasia. Robot-assisted hysterectomy was performed with a final pathological diagnosis of endometrial cancer (endometrioid carcinoma, Grade 1), stage 1A. She has remained disease-free for more than 12 months. Owing to advances in genetic medicine, prophylactic and therapeutic surgeries for hereditary cancers are increasing. To achieve an early diagnosis and treatment of Lynch syndrome-associated cancers, the importance of Lynch syndrome surveillance should be more widely recognized.

Correspondence to:
Naoki Horikawa, gorizou@kuhp.kyoto-u.ac.jp

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Introduction

Lynch syndrome (LS) is an autosomal dominant inherited disorder caused by a germline pathogenic variant in DNA mismatch repair genes, resulting in multi-organ cancer. LS carriers are reported to account for 0.35% of the general population and 3.0% among patients with endometrial cancer [1, 2]. In contrast to a 2.7% lifetime risk for the general population, LS carriers have a 13–47% lifetime risk of developing endometrial cancer [3]. Approximately, 75% of patients with LS-diagnosed endometrial cancer are at stage I, and they have an 88% 5-year survival rate [4]. The NCCN guidelines (NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal Version 3.2017) recommend endometrial biopsy and transvaginal ultrasonography (TVUS) for the surveillance of endometrial cancer in women with LS; however, the quality of the evidence is poor.

Here, we present the case of a 51-year-old woman with endometrial cancer who was treated using robot-assisted laparoscopic hysterectomy during early stage cancer detected during LS surveillance after her sister underwent multigene panel testing. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531837).

Case Presentation

A 51-year-old gravida zero woman, without any medical history and symptoms, was referred to the gynecology department for LS surveillance. Her last menstrual period was 6 months before her visit. The family history is shown in the family tree (shown in Fig. 1). Her 49-year-old sister was diagnosed with breast and rectal cancer at age 40, endometrial cancer at 43, and bladder cancer at 48.

Hereditary cancer syndromes, including hereditary breast-ovarian cancer syndrome and LS, were suspected. According to the NCCN guidelines (NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 2.2016), when the responsible gene cannot be narrowed down to one from a past medical history and family history, a multigene panel test is useful and cost-effective. Therefore, after genetic counseling, she underwent hereditary cancer panel testing (VistaSeq® Multi-Gene Hereditary Cancer Panels offered by Molecular Diagnostic Laboratory). The test assesses inherited mutations in 27 hereditary cancer genes (*APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FAM175A, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PRKAR1A, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*) which are involved in breast, colorectal, endometrial, breast, ovarian, prostate, and skin cancer. A pathogenic variant was found in the *MSH2* gene. As the proband was diagnosed with LS after genetic counseling, the present patient chose to undergo presymptomatic genetic testing for the *MSH2* variant, revealing the presence of the identical pathogenic variant (c.942 + 3A>T). As she was genetically diagnosed with LS, surveillance was initiated based on the NCCN guidelines (NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal Version 3.2017). Gastrointestinal and urological surveillance (upper gastrointestinal endoscopy, colonoscopy, *Helicobacter pylori* test, and urine cytology) showed no malignancies; however, during gynecologic surveillance, her endometrial cytology was classified as Papanicolaou class III, suggestive of, but not conclusive for, malignancy. Therefore, she underwent endometrial curettage with hysteroscopy that showed three smooth-surfaced endometrial polyps, which were pathologically diagnosed as atypical endometrial hyperplasia (shown in Fig. 2). Considering the result of her endometrial cytology and her diagnosis of LS, magnetic resonance imaging was conducted and showed no evidence of malignancy. Robot-assisted laparoscopic hysterectomy and bilateral salpingo-oophorectomy without lymph node evaluation were performed, with a final pathological

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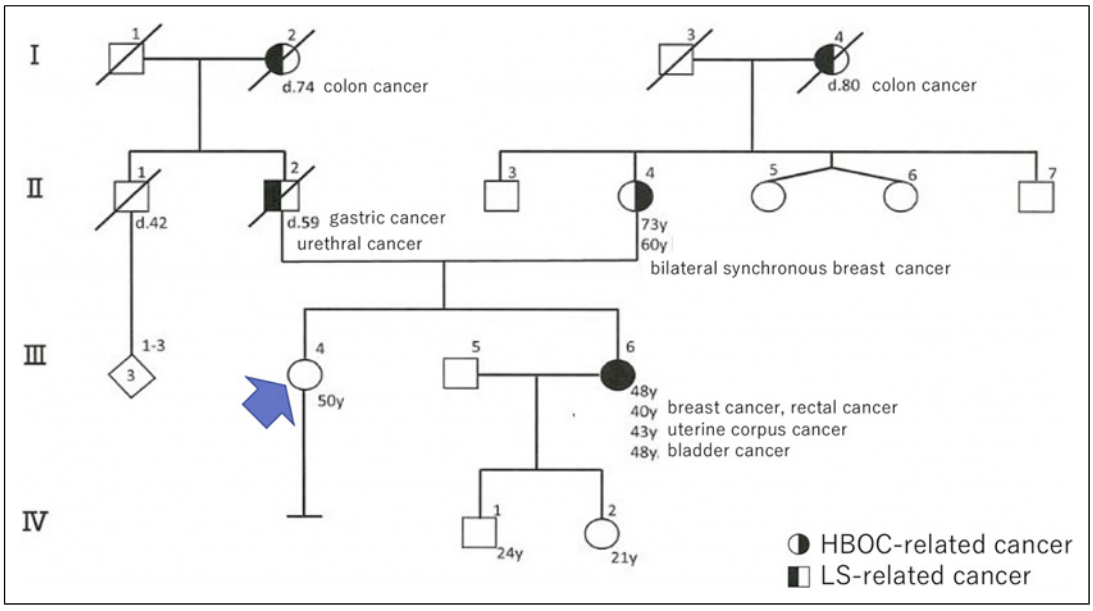

Fig. 1. The family history is presented as a family tree. The arrow indicates the present case. HBOC, hereditary breast-ovarian cancer syndrome; LS, Lynch syndrome.

diagnosis of endometrial cancer (endometrioid carcinoma, grade 1). She has remained disease-free for more than 12 months. Her niece and nephew (her sister's daughter and son) had genetic counseling and are considering genetic testing.

Discussion

Endometrial cancer surveillance has not been proven beneficial for women with LS [2]. The NCCN guidelines (NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal Version 3.2017) recommend endometrial biopsy every 1–2 years. Although routine TVUS is not recommended for premenopausal women, it may be considered for postmenopausal women based on the clinician's discretion. Screening by TVUS and/or hysteroscopy/endometrial biopsy revealed an endometrial cancer incidence of 3.9% in women with LS, and 64% of them were asymptomatic. The sensitivity and specificity of TVUS and endometrial biopsy are 34.4%/87.1% and 57.1%/66.7%, respectively [5]. Because of the low accuracy of detection techniques and slow progression of endometrial cancer, it can be difficult to demonstrate the best way of screening and effectiveness of surveillance.

The risk of developing endometrial cancer is different in patients carrying different DNA mismatch repair variants. In a prospective study of 1,942 mutation carriers without previous cancer, the endometrial cancer cumulative incidence rate for women with LS within 70 years was calculated as 34% in *MLH1* carriers, 51% in *MSH2* carriers, 49% in *MSH6* carriers, and 24% in *PMS2* carriers [6]. A systematic review of endometrial surveillance for patients with LS found that among 432 mutation carriers, 10 out of 25 endometrial cancer patients were *MLH1* carriers, 8 were *MSH2* carriers, and 3 were *MSH6* carriers. Mutated genes in the four remaining cases were not specified [5]. Mutation-specific risks guide differential management [7].

There is an increasing number of reports on prophylactic surgery. In 2006, Schmeler et al. [8] have reported that prophylactic hysterectomy with bilateral salpingo-oophorectomy was markedly effective. In 2021, prophylactic hysterectomy with bilateral salpingo-oophorectomy

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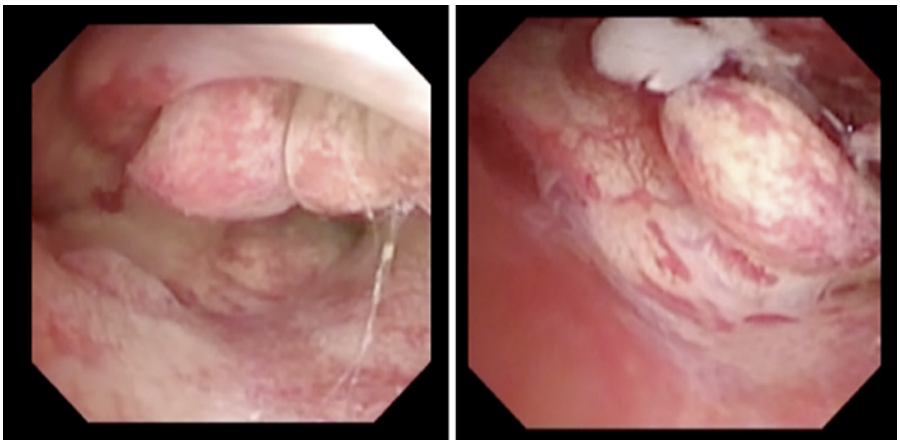

Fig. 2. Hysteroscopy shows three endometrial polyps with smooth surfaces without any signs of malignancy.

at age 30 was reported to be more cost-effective than annual surveillance [1]. Clinical practice guidelines recommend hysterectomy with bilateral salpingo-oophorectomy for women with LS [9, 10]. However, risk-reducing hysterectomy has not become widespread. For example, in 2021, risk-reducing hysterectomy was performed in only 28%, 25%, 15%, and 9% of patients (under age 50) carrying *MLH1*, *MSH2*, *MSH6*, and *PMS2* variants, respectively [10].

Moreover, endometrial surveillance remains uncommon in patients undergoing risk-reducing hysterectomy. Fedda et al. [11] (2020) have reported that out of 277 patients with LS who underwent risk-reducing hysterectomy, 23 had endometrial cancer, and only 46 had undergone preoperative endometrial surveillance, excluding those with unavailable data. Four patients with atypical endometrial hyperplasia and two with endometrial cancer were diagnosed preoperatively; in 1 patient, endometrial hyperplasia developed into endometrial cancer, and in another patient, endometrial cancer was diagnosed as atypical endometrial hyperplasia on final pathology [11]. In another case with the *MSH6* variant, preoperative endometrial sampling changed the surgical plan from only hysterectomy to hysterectomy with lymph node dissection, omentectomy, and peritoneal biopsies as the biopsy finding was endometrial serous adenocarcinoma [12]. If a risk-reducing hysterectomy is planned, preoperative endometrial sampling should be performed.

As genetic medicine advances, the prevalence of LS diagnoses is expected to increase further. However, because LS management has not yet been standardized, risk-reducing hysterectomy and endometrial surveillance are not widely accepted in clinical practice. The best way of surveillance and intervention should be investigated further and individualized.

Finally, another lesson learned from this case is that genetic testing can enable us to acquire crucial information about the patient's family. Although this patient had no medical history or symptoms, we could diagnose her cancer considering her sister's multigene panel testing that revealed a hereditary cancer syndrome. Genetic testing is informative not only for patients but also for their siblings.

As genetic medicine advances, prophylactic and curative surgeries for hereditary cancers are expected to increase. To ensure an early diagnosis, all gynecologists should share their knowledge of hereditary cancer surveillance and treatment with patients and their family members.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

Statement of Ethics

We reported this case report in compliance with the Helsinki Declaration. This study protocol was reviewed, and the need for approval was waived by the Ethics Committee of Shizuoka General Hospital. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There is no research support for this study.

Author Contributions

Maki Umemiya, Naoki Horikawa, and Kenzo Kosaka were in charge of the presented patient and treated her endometrial cancer. Maki Umemiya and Naoki Horikawa wrote the main manuscript, contributing to the conception and design, as well as revision, of the article. Ami Kanai, Ayaka Saeki, Kohei Ida, Satoru Makio, Teruki Yoshida, Mitsuru Tsuji, Rei Gou, and Hirohiko Tani were responsible for data acquisition and analysis. Takeshi Usui and Kenzo Kosaka read the article and gave suggestions to improve the manuscript.

Data Availability Statement

All data generated or analyzed in this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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