CASE REPORT
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ENDOMETRIAL CANCER SIX YEARS AFTER COLON CANCER IN LYNCH SYNDROME: SINGLE INSTITUTION CASE IN KOREA

Soo Youn Bae, MD[1*], Min Kyu Kim, MD[1*], Byoung-Gie Kim, MD, PhD[2]

[1]Division of Gynecologic Oncology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon; [2]Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Here, we present a case of endometrial cancer six years after colon cancer in a Lynch syndrome patient at one institution. A 36-year-old Asian woman underwent surgery for colon cancer and six years later she underwent surgery for endometrial cancer. Based on a family history of cancer, she underwent genetic testing, including gene sequencing, after she contracted the colon cancer. A microsatellite instability test was performed and showed an unstable final result. Gene sequencing (*MSH2*) revealed a mutation at c.2649 T>G (p.1883M). However, her follow-up was not normal. In the second operation, immunohistochemistry showed that her endometrium stained negatively for *MSH2*, consistent with the previous test. As far as we know, this is a first case of metachronous cancer sin Korea regarding Lynch syndrome in single institution. It is important for enterocolonists and gynecological oncologists to screen effectively to reduce the mortality and costs associated with these genetic malignancies.

Keywords: Lynch syndrome II; Endometrial neoplasms; Colonic neoplasms

Lynch syndrome is also called hereditary nonpolyposis colorectal cancer (HNPCC), and it increases the risk of endometrial cancer. Lynch syndrome patients and their siblings have a genetic risk of cancer resulting from a germline mutation in the DNA mismatch repair genes (*MSH2*, *MLH1*, and *MSH6* and less commonly, *PMS1* and *PMS2*) [1,2].

The screening tool used by clinicians to identify individuals who may benefit from further genetic evaluation lacks sensitivity. Therefore, the Bethesda Guidelines were developed for this purpose in 1997 and were revised in 2004 [3].

The current consensus of expert opinion recommends that women in Lynch-syndrome-affected families undergo surveillance for gynecological cancers, including an annual endometrial biopsy, ultrasonography, and tests for cancer antigen (CA) 125 [4].

Colorectal cancer screening in HNPCC has been shown to improve survival and the cost-effectiveness of treatments, but this has not been well studied for the associated endometrial and ovarian cancers [5,6].

Hysterectomy with bilateral salpingo-oophorectomy is a preventive strategy for women with HNPCC [7]. However, there are some obstacles to this treatment, including inadequate counseling, inadequate follow-up, and cost.

Here, we present a case of endometrial cancer six years after colon cancer in a patient with Lynch syndrome treated at one institution.

Case Report

A 36-year-old Asian woman visited a local clinic complaining of

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Corresponding author: Byoung-Gie Kim, MD, PhD
Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-3518 Fax: +82-2-3410-0630
E-mail: minkyukim@skku.edu
*Both authors contributed equally.

abdominal pain. Under a suspicion of a bowel problem, endoscopy was recommended.

A colonoscopy found a marginal elevated dirty-based ulcer with a stenotic lumen. The patient's carcinoembryonic antigen was 2.9 ng/mL, but her test results were otherwise normal. After preoperative work-ups, a right hemicolectomy was performed. The pathology results indicated an adenocarcinoma of the cecum, with moderate differentiation. The patient's lymph nodes were positive (11/36). The final diagnosis was stage IIIc colon cancer, so adjuvant chemotherapy (500 mg capecitabine) was prescribed. Considering her age and family history, she was genetically counseled and genetic tests (gene sequencing) were performed. Four family members had suffered cancer (Fig. 1): her mother had had ovarian cancer at 53 years of age; her father had had stomach cancer, but there was no information regarding the onset age; her maternal grandmother had had breast cancer; and her paternal grandfather had had liver cancer at 64 years of age. These also meet the Amsterdam and Bethesda criteria. According to the diagnostic algorithm, a microsatellite instability test was performed and showed an unstable final result: BAT 25 unstable, BAT 26 unstable, D5S346 unstable, D17S250 stable, and D2S123 unstable. Gene sequencing (*MSH2*) revealed a mutation at c.2649 T>G (p.1883M) (Fig. 2). But after genetic counseling, instead of hysterectomy and bilateral salpingo-oophorectomy regular transvaginal ultrasonography, gynecologic exam and tumor marker was recommeded. Patient didn't want prophylactic surgery because lack of importance about cancer risk. The patient lived far from the hospital, so follow-up at a local clinic was recommended. Six years later, she visited the local gynecological clinic with vaginal bleeding, at the age of 41 years. Under suspicion of an endometrial pathology, a biopsy was performed, which revealed an endometrioid adenocarcinoma. The patient visited Samsung Medical Center and underwent a hysterectomy, salpingo-oophorectomy, and pelvic lymph-node dissection. The pathology revealed an endometrioid adenocarcinoma, grade I/III, with cervical stromal invasion, but no lymph-node metastasis (0/16).

The patient received vaginal brachytherapy. Immunohistochemically, her endometrium stained negatively for *MSH2* (Fig. 3).

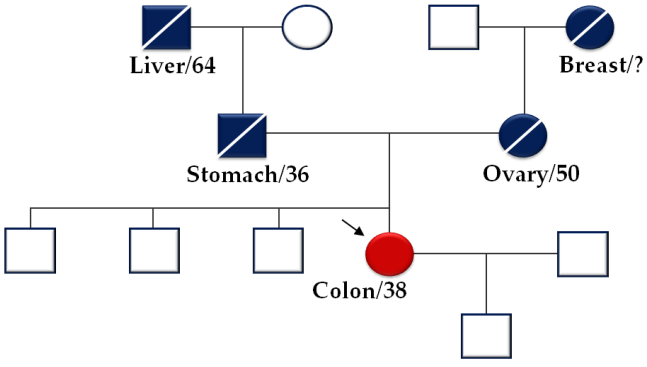

Fig. 1. Family history of cancer.

Discussion

This case demonstrates that a second cancer can occur in a patient with Lynch syndrome after a long period. As far as we know, this is a first case of metachronous (multiple separate, such as multiple primary cancers developing at intervals) cancers in Korea regarding Lynch syndrome in single institution. Gynecological oncologists and enterocolonists can cooperate to not only prevent but detect early recommend preventive surgery. With the advances in molecular biology now available for the diagnosis of genetic cancers, clinicians can help to prevent these cancers by counseling

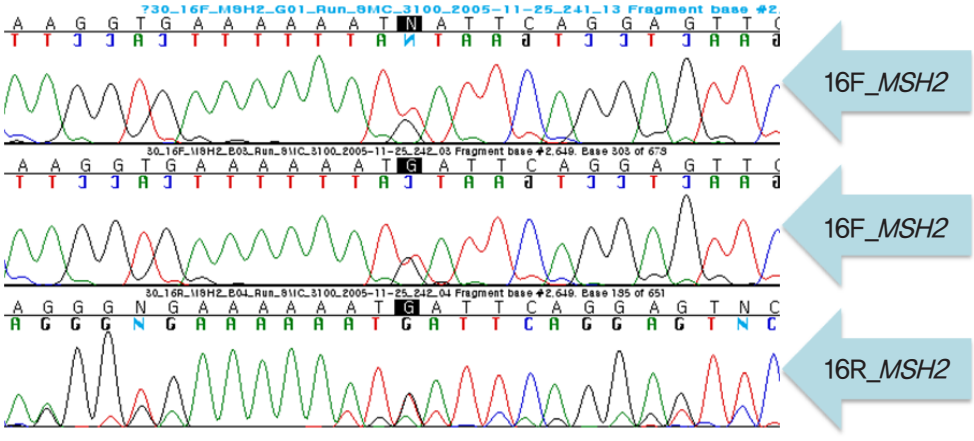

Fig. 2. Gene sequencing result.

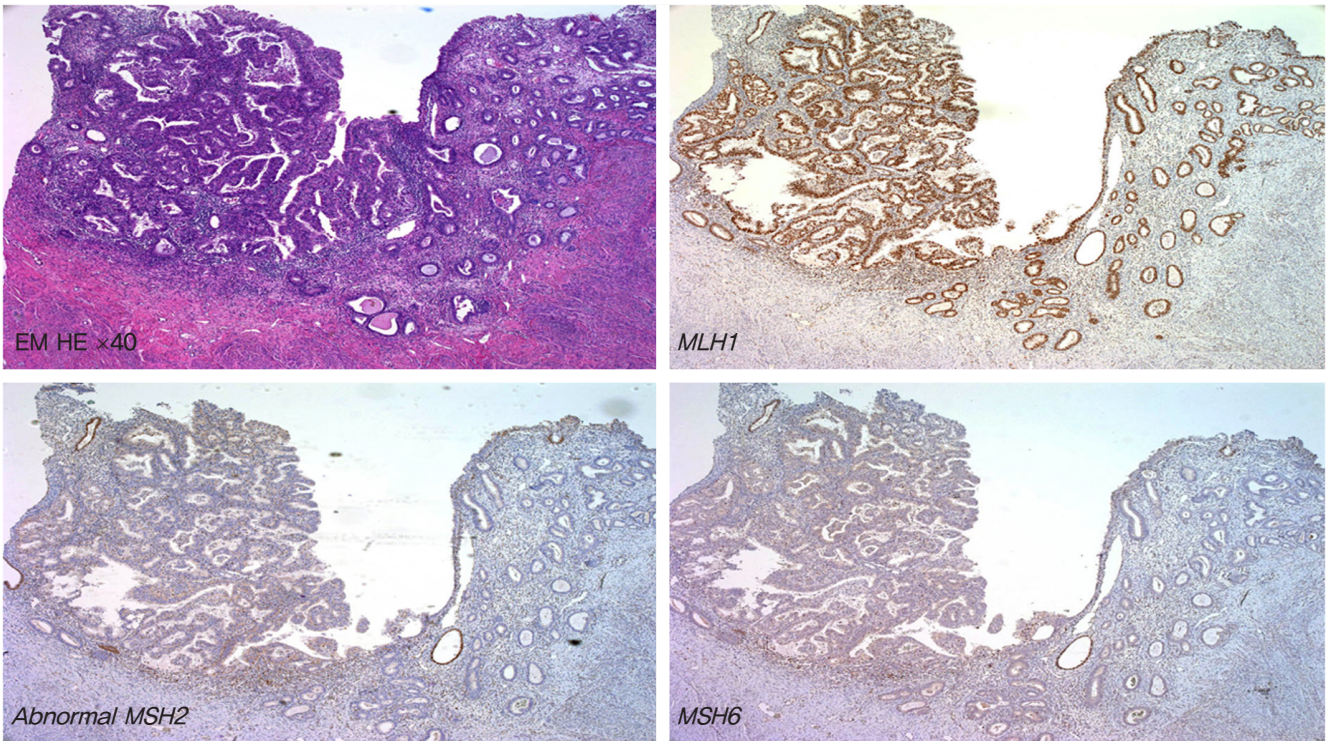

Fig. 3. Immunohistochemistry of endometrium (H&E, ×200).

patients and prescribing adequate and appropriate tests.

Proper genetic screening and counseling should be offered to at-risk patients to prevent second cancers in Lynch syndrome patients. Enterocolonists and gynecological oncologists should cooperate to effectively screen for Lynch syndrome and thus prevent further malignancies.

Women who are suspected of HNPCC syndrome should be referred for genetic counseling, and those at very high risk on the basis of their family history or mutation status should undergo screening for endometrial cancer. Screening colonoscopy, either annual or biennial, commencing at an age of 20 to 25 years, is known to reduce mortality in these patients [8,9].

Six years elapsed between the diagnosis of colon cancer in this case and the diagnosis of a gynecological cancer. Women who survive an initial colon cancer but are not identified as having HNPCC syndrome cannot take advantage of screening and prophylactic surgical options for endometrial and ovarian cancers. According to the consensus opinion, a pelvic examination, transvaginal ultrasonography, endometrial biopsy, and CA 125 are recommended annually, beginning at an age of 25 to 35 years in HNPCC patients [10].

Women diagnosed with colon cancer who are known mutation carriers or have a high likelihood for HNPCC syndrome can choose total abdominal hysterectomy and bilateral salpingo-oophorectomy at the time of surgery for their colon cancer. In one study, early-onset colorectal cancer (below 45 years of age) was more likely to indicate Lynch syndrome than late-onset disease [11]. In this case, she was 36 years old when she underwent colon surgery.

We must develop clear criteria with which gynecological oncologists and enterocologists can triage patients for genetic counseling and testing based on their disease status, economic status, religion, educational status, insurance coverage. More information is also required about the appropriate genetic tests (metylation test, microsatellite instability and gene sequencing) for both counseling about risk of another cancer in offspring and relative.

In conclusion, enterocolonists and gynecological oncologists share some responsibility in preventing second cancers in patients with Lynch syndrome. Patients should be given the correct genetic tests and counseled appropriately because these actions are important in reducing cancer mortality and costs.

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린치증후군 대장암 환자에서 6년 후에 발생한 자궁내막암 증례

성균관대학교 의과대학 [1]삼성창원병원, [2]삼성서울병원 산부인과학교실
배수연[1], 김민규[1], 김병기[2]

린치증후군은 자궁내막암과 대장암을 일으키는 유전성질환이다. 한 병원에서 두번 암 진단과 수술을 받은 환자에 대한 연구이다. 유전암에 대한 위험과 예방방법에 대한 부인종양 의사와 대장암 의사의 협진과 노력이 있어야 될 것이다.

중심단어: 린치증후군, 자궁내막암, 대장암