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Case Report

Case Report of Menopausal Woman Diagnosed with Endometrial Cancer after Colon Cancer with Germline Mutation in *MSH6* in Korea

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We present a case of an endometrial cancer patient with germline mutation in MutS homolog 6 (*MSH6*), associated with Lynch syndrome. A 60-year-old Korean woman had a personal history of colon cancer 23 years ago. She also had a family history of endometrial cancer and colon cancer of her sisters and brothers. Immunohistochemistry was negative for MutL homolog 1 (*MLH1*) and positive for MutS homolog 2 (*MSH2*). Based on these findings, she underwent genetic counseling and testing that revealed a frameshift germline mutation at *MSH6* (c. 3261dupC). **(J Menopausal Med 2017;23:69-73)**

Key Words: Endometrial neoplasms · Germ-line mutation · Hereditary nonpolyposis · Lynch syndrome

Introduction

Lynch syndrome is one of the hereditary cancer syndromes caused by germline mutation in the DNA mismatch repair (MMR) genes.[1] Individuals affected by Lynch syndrome have a high risk of colon cancer, endometrial cancer and other cancers of ovaries, small bowel, urothelium, biliary tract, and stomach.[2,3] Family history is most important in identifying individuals who are affected by Lynch syndrome, and the Bethesda guidelines and Amsterdam criteria II are helpful in analyzing the data.[1] According to the National Comprehensive Cancer Network (NCCN) guidelines, Lynch syndrome-affected individuals should be kept under surveillance for gynecologic malignancies and other cancers.[4] Prophylactic hysterectomy and bilateral salpingo-oophorectomy (BSO) is an optional strategy to reduce the risk of a gynecologic tumor for women who have completed childbearing.[4] Here, we present a case of endometrial cancer with germline mutation in MutS homolog 6 (*MSH6*), associated with Lynch syndrome that was diagnosed 23 years after the diagnosis of colon cancer.

Case Report

A 60-year-old Korean woman visited the Comprehensive Gynecologic Cancer Center with the chief complain of continuous vaginal spotting for 9 months. The result of transvaginal ultrasonography was a suspicious lesion of endometrial pathology. Endometrial biopsy was performed and the result was high grade serous adenocarcinoma. Tumor markers were in normal range (carcinoembryonic

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antigen [CEA] 0.68 ng/mL, cancer antigen 125 [CA-125] 14.6 u/mL). About 1.6 cm-sized endometrial mass was noted on a pelvic magnetic resonance imaging, and there was no evidence of metastasis in positron emission tomography-computed tomography. Under impression of early-staged endometrial serous carcinoma, she underwent a hysterectomy with BSO, pelvic and para-aortic lymph node dissections, omentectomy, appendectomy, and washing cytology. The pathologic result was high grade serous adenocarcinoma of the endometrium without any metastasis indicating the International Federation of Obstetrics and Gynecology (FIGO) stage IA (myometrial invasion 7/20 mm, negative lympho-vascular space invasion and negative metastatic lymph nodes: 0/25). The results of immunohistochemistry (IHC) of the endometrial cancer showed negative staining for MutL homolog 1 (*MLH1*) and positive staining for MutS homolog 2 (*MSH2*). She had received 6 cycles of platinum-based adjuvant chemotherapy.

She had been diagnosed with metachronous early-staged colon cancer 23 years ago at another institution. Her sibling had a history of cancers. (Fig. 1A). Her brother was diagnosed with colon cancer in his 50's, and the older brother had gastric cancer in his 30's. Her 2 younger sisters were diagnosed with endometrial cancer at the age of 56 and 53 respectively. Considering the family history, genetic counseling and genetic testing was performed. The germline mutation at *MLH1* and *MSH2* genes was not detected. However, a frameshift variation was detected in exon 5 of *MSH6* (NM_000179.2:c. 3261dupC), which was interpreted as creating a new reading frame at Phe1088 and encountering premature stop codon at the 5th position from the new reading frame (p. Phe1088Leufs*5; Fig. 1B). The variation was classified as pathogenic in the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) database (www.insight-group.org). Screening endoscopy and colonoscopy was performed and the results were normal. We

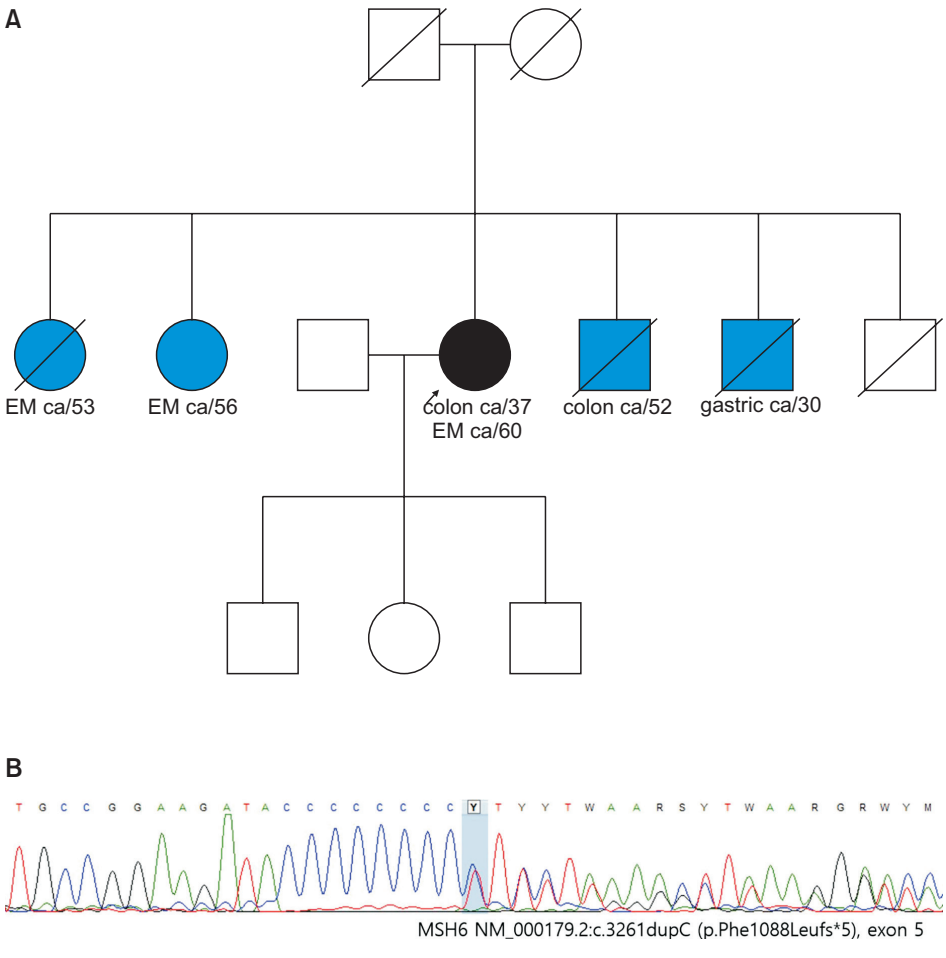

Fig. 1. (A) Pedigree of the patient. (B) Gene sequencing result of *human MSH6*. EM: endometrial, Ca: cancer.

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have planned genetic counseling and testing for the other family members.

Discussion

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant cancer-susceptibility disorder, caused by germline mutation in 4 DNA MMR genes (*MLH1*, *MSH2*, *MSH6*, and postmeiotic segregation increased 2 [*PMS*]).[1] Nearly 90% are located in *MLH1* and *MSH2*, and approximately 10% in *MSH6* and *PMS2*.[2,3] Approximately 3% to 5% of endometrial cancer is associated with Lynch syndrome.[5] When affected by Lynch syndrome, the lifetime risk of endometrial cancer is 16% to 60%,[4,6] *MSH6* mutation presents a higher relative risk of endometrial cancer than *MLH1* or *MSH2* mutation.[7] Lynch syndrome is generally suspected if there is family history of Lynch syndrome-associated cancers using clinical criteria or a tumor phenotype showing negative in IHC or high DNA microsatellite instability (MSI).[3,8] Therefore, detailed family history taking is important for identifying individuals who have increased risk of Lynch syndrome.

The patients with Lynch syndrome were identified by family history based on clinical criteria such as Amsterdam II or Bethesda criteria, and genetic pre-screening test (IHC staining or MSI test).[4] After identification individual with hereditary predisposition, genetic test will be performed.[9] This flow would be best option for diagnosis of Lynch syndrome in current medical environment. However, in Korea, the definite guideline to screen and genetic test is not established and there is little study for germline mutations of Lynch syndrome in endometrial cancer patients.[10,11] Heo, et al.[12] had reported the 55-year old woman of endometrial cancer with *MSH2* germline mutation without family history of cancer in Korea. The patient could be identified by IHC staining (*MSH2* negative) and diagnosed Lynch syndrome by genetic test. Compared with the present case, current case was diagnosed of double primary endometrial and colorectal cancer and there were family histories of Lynch syndrome-related cancers.

The present case demonstrates endometrial cancer 23 years after the diagnosis of colon cancer associated with Lynch syndrome. She is one of the first Lynch syndrome cases of *MSH6-related* metachronous cancer (colon cancer/endometrial cancer) in Korea to our knowledge. However, she has not sufficiently fulfilled the Amsterdam criteria II (Table 1) because a successive generation was not affected by cancer. IHC test was limited to *MLH1* and *MSH2* not *MSH6* and *PMS2* and MSI was not tested. Fulfillment the suspected HNPCC[13] of her family history (Fig. 1A) was the only strongly suspected key to proceed further genetic test other than *MLH1* or *MSH2*.

For individual affected by Lynch syndrome, the colonoscopy every 1 to 2 years, esophagogastroduodenoscopy with extended duodenoscopy every 3 to 5 years, annual urinalysis could be recommended for surveillance of colon, gastric, small bowel and urothelial cancer.[4] The surveillance for the present case is followed as the guideline including transvaginal ultrasound every year and surveillance of recurrence of endometrial cancer.

Endometrial cancer is often classified into type I (endometrioid cell) and type II (serous, clear, mucinous and mixed cell) subtypes, which reflect general characteristics of its clinicopathologic spectrum. Type II neoplasms are generally associated with more aggressive clinical behavior than type I tumors.[14] While type II tumors comprise 10% to 20% of endometrial carcinomas, they account for 40% of deaths from the disease.[15] The relationship of Lynch syndrome to histologic types of endometrial cancer was

Table 1. Revised criteria for clinical HNPCC/Lynch syndrome (Amsterdam criteria II)

At least three relatives with an HNPCC-associated cancer (colorectal, endometrial, small bowel, ureter or renal pelvis cancer).
One should be a first-degree relative of the other two.
At least two successive generations should be affected.
Familial adenomatous polyposis should be excluded in the colorectal cancer case(s), if any.
Tumors should be verified by pathologic examination.

HNPCC: hereditary non-polyposis colorectal cancer
[Reprinted from "Suspected HNPCC and Amsterdam criteria II: evaluation of mutation detection rate, an international collaborative study", by Park JG, Vasen HFA, Park YJ, Park KJ, Peltomaki P, de Leon MP, et al., 2002, Int J Colorectal Dis, 17, pp.109-14. Copyright 2001 by the Springer-Verlag. Reprinted with permission].

not exactly known. There has been controversy regarding incidence of each histological type of endometrial cancer with Lynch syndrome.[16] The histological subtype of endometrial cancer associated with Lynch syndrome presents a higher frequency of type I endometrial cancer than type II cancer.[16] However, the other studies showed that higher incidence of type II cancer in Lynch syndrome group than control groups.[17] The histologic type of the present case is serous endometrial cancer. Her living sister diagnosed neuroendocrine endometrial cancer, one of the rare type II cancers. We do not know the MMR genetic mutation status of this sister. It might be consider that there is a likelihood of specific pathophysiological relationship between *MSH6* and type II endometrial cancer, although there are no published studies that demonstrate this relationship at present.[17] Further studies about the correlation between histological type of endometrial cancer with Lynch syndrome and MMR genetic mutation gene types (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) are needed.

The genetic test of the present patient's family has not yet been performed because of limited medical insurance options in Korea. It would be more desirable clinical environment to freely prescribed to the patient genetic test and pre-screening test as guidelines. Improvements in the aspect of domestic insurance and medical environments are needed to manage cancer risk effectively for patients and their families affected by Lynch syndrome.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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