JMM
pISSN: 2288-6478, eISSN: 2288-6761
http://dx.doi.org/10.6118/jmm.2013.19.3.143
Journal of Menopausal Medicine 2013;19:143-146

Case Report

A Case of Perimenopausal Endometrial Cancer in a Woman with MSH2 Germline Mutation

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Lynch syndrome is a genetic malignancy syndrome affecting the colon, endometrium, and other organs. It is difficult to find a Lynch syndrome patient without any family history of cancer. We have recently examined an endometrial cancer patient with a MSH2 gene mutation without a family history of cancer. A 55-year old Korean woman was admitted to a local clinic for vaginal bleeding. An endometrial biopsy revealed the presence of adenocarcinoma (endometrioid type, grade 1). After surgical staging, no further adjuvant therapy was required. Analysis of the tissue using immunohistochemistry (IHC) showed the endometrium stained negatively for MSH2. Microsatellite instability (MSI) was analyzed for five markers. The patient was scored as unstable. Further, additional gene sequencing revealed one missense mutation in c.23C > T (p.Thr8Met). This is the first case of Lynch syndrome endometrial cancer in Korea in which the patient does not have any family history of cancer. **(J Menopausal Med 2013;19:143-146)**

Key Words: Endometrial neoplasms, Lynch syndrome

Introduction

Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer [HNPCC]) results from mutations in mismatch repair genes (MLH1, MSH2, MSH6, or PMS2) and is associated with a variety of extra-colonic sites, like endometrium, stomach, ovaries, urinary tract and kidneys, biliary tract, pancreas, small intestine, brain and skin.[1] Endometrial cancer is the most common malignant disorder observed after HNPCC.

Considering that Lynch syndrome is an autosomal-dominant inherited cancer syndrome, identifying a family history using genetic counseling can lead to further tests based on the current guidelines (revised Amsterdam[2] or Bethesda[3] criteria). And identification of individuals who have increased risk of occurring hereditary cancers would enable screening and early detection of cancer, which may reduce disease-specific mortality. Recording a patient's family history is the first step in the work-up of Lynch syndrome patients. However, recording an accurate family history is often neglected or inconsistent.[4,5] It can be challenging to advise patients to proceed with additional testing when they do not have a family history of cancer.

Screening for colorectal cancer in HNPCC has been proven to improve survival and the cost-effectiveness of treatments, but the benefits of screening for gynecological cancers in Lynch syndrome patients have not yet been proven. Additionally, there is no consensus regarding the

Received: August 15, 2013 **Revised:** September 18, 2013 **Accepted:** September 18, 2013
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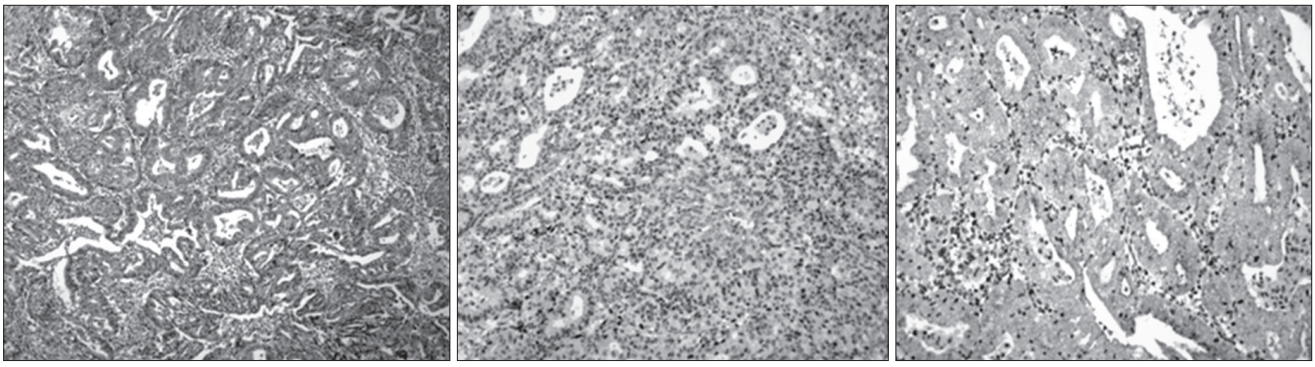

Fig. 1. Immunohistochemistry results (× 200).

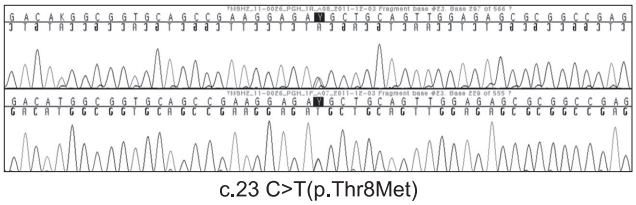

Fig. 2. Gene sequencing result.

optimal screening tests to perform based on country or patient ethnicity.

Here, we present a case of endometrial cancer in a Lynch syndrome patient that did not have a family history of cancer.

Case Report

A 55-year-old Korean woman was admitted to a local clinic for vaginal bleeding. An endometrial biopsy revealed the presence of adenocarcinoma (endometrioid type, grade 1). The patient was referred to Samsung Changwon Hospital for further evaluation and treatment. The patient received pelvic magnetic resonance imaging, computed tomography scan, and other diagnostic tests. The patient had a cancer antigen 125 (CA 125) level of 9.06 U/mL and no other abnormal masses were visible in imaging tests. Complete surgical staging including total hysterectomy, bilateral salpingo-oophorectomy, washing cytology, and pelvic lymph node dissection was performed. The operation was concluded after confirming a frozen biopsy of the pelvic lymph node was not cancerous.

Although this patient had no family history of cancer (her three sisters and parents were alive without any cancer diagnoses at the time of counseling), screening immunohistochemistry (IHC; MLH1, MSH2) was performed due to the genetic risk of Lynch syndrome. The results indicated that MLH1 was positive in 90% f the sample and MSH2 was negative (Fig. 1). The tissue pathology reported the tumor stage was IA and adjuvant treatment was not recommended.

According to diagnostic algorithms and after genetic co-unseling, microsatellite instability (MSI) and gene sequencing were performed. MSI was analyzed for five markers (BAT25, BAT26, D2S123, D5S346, and D17S250). The results indicate there were two unstable markers (BAT25 and BAT26), and the patient was scored MSI-high (unstable). Further gene sequencing analyses revealed one missense mutation (c.23C > T [p.Thr8Met]) (Fig. 2). Therefore, a gastroenterologist was involved in the patient's counseling. A screening endoscopy was performed and the results were normal.

Discussion

This case demonstrates that Lynch syndrome-related cancer can occur in a patient despite the lack of any family history. This is the first case report of an endometrial cancer patient with a Lynch syndrome germline mutation without family history in Korea.

The risk of developing a second cancer is approximately

25% after 10 years and 50% after 15 years following the initial diagnosis of Lynch syndrome.[6] Therefore, the patient and her family were offered cancer screening and genetic counseling.

Approximately 2% to 5% of endometrial cancers may be caused by an inherited susceptibility.[7] In Lynch syndrome carriers, the lifetime risk of endometrial cancer has been estimated to be 42 to 54%, and may equal or exceed the risk of colorectal cancer.[8]

Lynch syndrome is caused by a germline mutation in one of the DNA mismatch repair genes (MLH1, MSH2, MSH6, and PMS2), and accounts for the majority of inherited cases.[7]

In younger patients, the incidence of endometrial cancer increases to 9% and better survival rates.[9,10]

Information on family history is important for identifying individuals that could benefit from genetic counseling and predictive genetic testing. However, other genetic screening tests are effective in selecting suitable patients. The results from this patient's test (IHC and MSI) were abnormal. After counseling and describing the risk and benefits obtained from these results, further confirmative tests for detection of a pathogenic mutation in one of the DNA mismatch repair genes were performed with the patient's permission.

With the advances in molecular biology now available for the diagnosis of genetic cancers, clinicians can help prevent these cancers by counseling patients and prescribing adequate and appropriate tests.

In known mutation carriers without any colorectal adenomas, screening colonoscopy appears to be the most reasonable choice.[11] However, prophylactic subtotal colectomy remains an option for patients who have significant anxiety about cancer risk or concern about the safety of repeated colonoscopies. Additionally, colectomy can be used if the patient is unable to receive periodic surveillance colonoscopies.[12]

More information is required to determine the appropriate genetic tests for counseling and prevention according to the country and ethnicity of the patient.

It is also important to identify patients with Lynch syndrome because families of mutation carriers may benefit from genetic counseling, testing, and intensified cancer surveillance.

In conclusion, gynecological oncologists should provide information of the genetic cancer risk to endometrial cancer patients in an effort to prevent second cancers in patients and family with Lynch syndrome. Patients should undergo the correct genetic tests and should be counseled appropriately, which is important for reducing cancer mortality and costs.

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