Case Report
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Endometrial cancer occurence five years after breast cancer in BRCA2 mutation patient

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We recently experienced a case of endometrial cancer 5 years after the diagnosis of breast cancer in a patient with a mutation in the BRCA2 gene. A 55-year-old Korean woman who had a past history of breast cancer in her 50s underwent an operation for endometrial cancer. Final pathology confirmed stage Ia, and no adjuvant treatment was performed. After surgery, considering her history of sequential cancer occurrence, genetic counseling was offered. The result showed the BRCA2 variation of unknown significance mutation. This is the first case report of sequential cancers (endometrial and breast) in a patient with a BRCA2 mutation among a Korean population.

Keywords: BRCA; Breast neoplasms; Endometrial neoplasms

Introduction

Endometrial cancer is one of the most common and curable gynecologic cancers. It usually occurs in women over the age of 50 years. The risk factors for endometrial cancer are associated with exposure to unopposed estrogen, obesity, diabetes mellitus, and hypertension [1].

Endometrial cancer has been divided into two subtypes. Type I (endometrioid histology) is estrogen-related and is low grade with estrogen receptor positivity; it typically arises from atypical complex hyperplasia. Type II (serous, clear cell carcinoma) is not estrogen-related and is known to be associated with its precursor, endometrial intraepithelial carcinoma, adjacent to an atrophic endometrium. Genetic background research of these two subtypes revealed distinct molecular mechanisms. For examples, PTEN or β-catenin gene mutations are common in type I. However, mutations in HER2/neu, p53, p16, e-cadherin, and a loss of heterozygosity are found in type II [2].

Breast cancer genes 1 and 2 (BRCA1 and BRCA2) are the most well-known genes linked to an increased risk of breast and ovarian cancers, as well as several other types of cancer [3]. The prevalence of BRCA1/2 mutations among cancer patients may differ according to region and ethnicity from 1.1% to 39.7% [4]. Lim et al. [5] examined BRCA1 and BRCA2 germ line mutations in Korean ovarian cancer patients and reported that 13 deleterious mutations (11 in BRCA1 and 2 in BRCA2) were detected among 54 patients.

In breast cancer, the average lifetime risk is 65% and 45% in women with BRCA1 and BRCA2 mutations, respectively. In ovarian cancer, the average lifetime risk is 39% and 11% in women with BRCA1 and BRCA2 mutations, respectively [6].

Recently, BRCA genes have been studied in association with endometrial cancer. There are only several case reports published in relation with endometrial cancer among BRCA gene carriers, and no genetic basis has been established. Levine et al. [3] studied the risk of endometrial carcinoma associated with BRCA mutations and concluded that the lifetime risk of endometrial carcinoma is not associated with BRCA mutation.

Our case is the first evidence of a possible genetic association between BRCA2 mutation and endometrial cancer in the Korean population. This finding can be helpful information for the diagnosis of genetic cancers by providing possible insight

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to patients regarding the association of endometrial cancer with the BRCA2 mutation.

Case report

A 55-year-old woman was referred to the Samsung Changwon Hospital for further treatment of biopsy proven endometrial cancer. The patient then underwent abdominal-pelvic computed tomography and magnetic resonance imaging that demonstrated an approximately 15-mm round mass in the ventral wall of the uterus without any evidence of distant or lymph node metastasis.

She underwent surgical staging, including laparoscopic assisted vaginal hysterectomy, bilateral salpingo-oophorectomy, laparoscopic pelvic lymph node dissection, and washings.

The final pathology confirmed stage I endometrioid adenocarcinoma with squamous differentiation, grade 1/III, with endometrial stromal invasion but no myometrial invasion. And there was no pelvic lymph-node metastasis (0/5).

Her medical history revealed that she had been diagnosed with left breast invasive ductal carcinoma in her 50s for which she underwent a modified radical mastectomy. After that, she was treated with letrozole from December 2009 to February 2014.

Her father died of stomach cancer in his 60s. Considering her past history of breast cancer, she received genetic counseling with informed consent for testing for BRCA1 and BRCA2 germline mutations. Then, the genetic tests were performed.

Immunohistochemistry (IHC) analysis showed that the endometrial/breast tissue stained positive for BRCA2 (10%/30%) by proportion (Fig. 1). A previous study did not prove the availability of IHC detecting BRCA mutation, but genetic risk assessment, including family history and IHC, needs additional investigation. She was offered cancer risk assessment based on cancer type, family and personal cancer history, and IHC results.

On her blood sample for genetic testing, a BRCA2 mutation was detected. A missense mutation from threonine to isoleucine due to a 1889 site nucleotide substitution from cytosine to thymine of BRCA2 gene was identified (c.1889C>T [p.Thr630Ile]) (Fig. 2).

Discussion

Among the Korean population, this is the first case that demonstrates endometrial cancer after breast cancer in a patient with a BRCA2 mutation. In addition, this case shows possible genetic relationships between breast cancer and endometrial cancer.

Germ line mutations in BRCA1 or BRCA2 increase the risk of breast cancer by 40% to 80% and ovarian cancer by up to 11% to 40% [7]. Other cancers such as pancreatic, gallbladder, gastric, malignant melanoma, and prostate have been reported to be related to BRCA1 and 2 mutation [8-10]. Approximately 5% of endometrial cancer cases are caused by germline mutations [11]. A recent study showed that the BRCA mutation is related to an increased endometrial cancer risk in addition to ovarian carcinoma among gynecologic malignancies [1,3].

This is first case of a patient with a BRCA2 variation of unknown significance mutation who developed endometrial cancer after breast cancer diagnosis. It is hard and expensive to offer genetic testing for all cancer patients. Considering her early breast cancer diagnosis in her 50s and her family history of cancer (father with stomach cancer), genetic counseling and

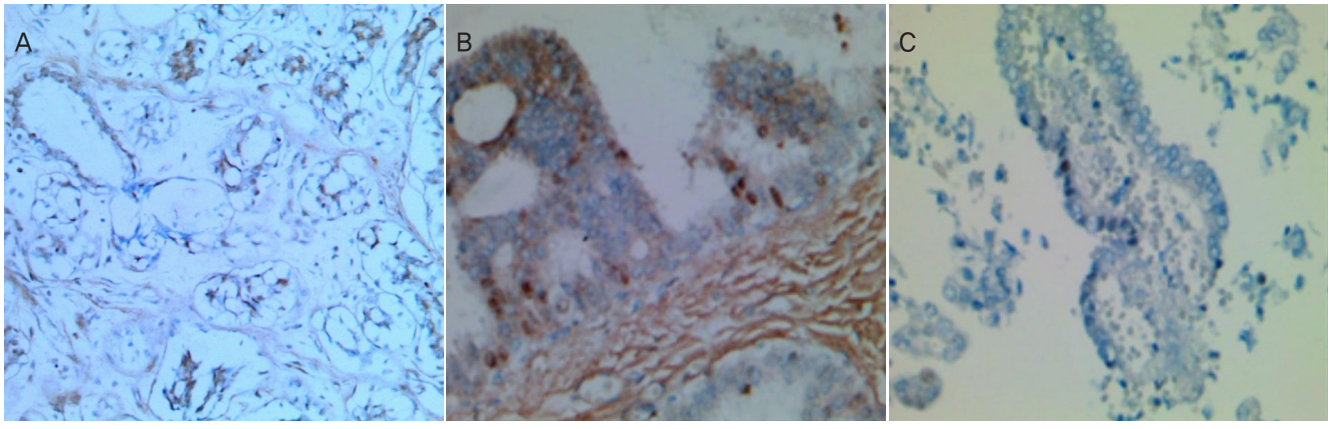

Fig. 1. Immunohistochemistry of BRCA2 (×200). BRCA2 reagent (Abcam, ab27976). (A) Control (breast), (B) breast, and (C) endometrium.

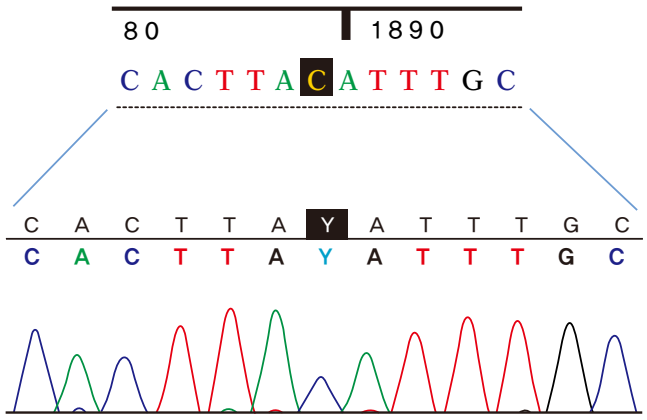

Fig. 2. Gene sequencing results.

testing should have been offered to her.

There are three options for BRCA mutation carriers: risk-reducing salpingo-oophorectomy (RRSO), screening for sequential cancer, and chemoprevention. Early detection through CA-125 and transvaginal ultrasound are not effective prevention strategies for ovarian cancer. Chemoprevention with low dose oral contraceptives decrease ovarian cancer risk by as much as 44% to 60% [12].

Bilateral risk reducing mastectomy is known to decrease breast cancer risk by 90% in BRCA mutation carriers. RRSO in BRCA mutation carriers decreases ovarian cancer risk as well as improving overall mortality [13].

Prophylactic hysterectomy may be offered at the time of RRSO to reduce endometrial cancer risk in patients with BRCA mutations with the additional risk factor of tamoxifen use [14].

Risk-reducing surgery can be an emotional and economical challenge to patients, but careful and exact genetic risk assessment and counseling should be offered to appropriate patients with cooperation with breast surgeons and gynecologic oncologists.

Conflict of interest

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

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