HBOC syndrome with an uncharacterized variant in the *BRCA1* gene in a patient diagnosed with endometrial cancer after surgery for bilateral breast cancer: A case report

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Abstract. The association between endometrial cancer and the *BRCA1* and *BRCA2* genes is not fully understood, and the risk elevation of endometrial cancer in patients with hereditary breast and ovarian cancer (HBOC) is not understood. The present report examines a rare case of HBOC syndrome and an uncharacterized variant of the *BRCA1* gene in a patient diagnosed with endometrial cancer. A 46-year-old woman, gravida 1 para 1, was referred to Wakayama Medical University Hospital (Wakayama, Japan) because positron emission tomography/computed tomography (PET/CT) showed a high FDG uptake in the corpus uteri and the left ovary. PET/CT was performed just after mastectomy for left-sided breast cancer (triple negative). The patient had previously undergone partial mastectomy for right-sided breast cancer (triple negative) and was treated with radiation therapy to the right residual breast when she was 39 years old. Laparoscopic hysterectomy and bilateral adnexectomy were performed, and the histological diagnosis was endometrioid carcinoma, grade 1. Her germline *BRCA* status was tested by blood examination and the result was 'NM_007294.4(BRCA1):c.49G>C (p.Ala17Pro)'. The variant was evaluated as 'likely pathogenic'. The patient was diagnosed with HBOC syndrome and endometrial cancer, pT1ANxM0. The patient had no recurrence of breast or endometrial cancer 16 months after gynecologic surgery.

Introduction

According to the National Cancer Institute, hereditary breast and ovarian cancer (HBOC) syndrome is defined as an inherited disorder in which the risk of breast cancer (especially before the age of 50) and ovarian cancer is higher than normal. HBOC syndrome is known to exhibit an autosomal dominant inheritance. Most patients with HBOC syndrome exhibit certain mutations in the *BRCA1* or *BRCA2* genes. Patients with HBOC syndrome may also have an increased risk of other types of cancer, including pancreatic cancer, prostate cancer, and melanoma (1). Among patients with breast cancers between 35 and 64 years old in the USA, 2.4 and 2.3% carried deleterious mutations in *BRCA1* and *BRCA2*, respectively (2). Among patients with ovarian cancer, 15% had mutations in *BRCA1* or *BRCA2* (3). In Japan, all patients with breast and ovarian cancer are recommended to undergo a germline *BRCA* test.

The association between endometrial cancer and the *BRCA1* and *BRCA2* (*BRCA1/2*) genes is unresolved, and the risk elevation of endometrial cancer in HBOC patients is not understood.

We examined a rare case of HBOC syndrome and an uncharacterized variant of the *BRCA1* gene in a patient, who was diagnosed with subclinical endometrial cancer by positron emission tomography/computed tomography (PET/CT) imaging after surgery for bilateral breast cancer.

Case report

A 46-year-old woman, gravida 1 para 1, was referred to our hospital because PET/CT showed a high FDG uptake (SUVmax=4.87 and 3.22, respectively) in the endometrium and the left ovary (Fig. 1). PET/CT was performed just after mastectomy for left-sided breast cancer (pT1bN1aM0, triple negative). She had previously undergone partial mastectomy (ypT0N0M0) to treat right-sided breast cancer following neoadjuvant chemotherapy (cT2N0M0, triple negative), and then she was treated with radiation therapy to the right residual breast when she was 39 years old. Her mother was diagnosed with breast cancer at the age of 38. Her father had gastric cancer. The other relevant clinical information of the present patient is described in Table I.

The endometrial biopsy revealed atypical endometrial hyperplasia. MRI diffusion-weighted image (b=1,000) showed a high intensity in the endometrium, whereas myometrial

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invasion was not observed (Fig. 2). No metastatic lesion was detected by PET/CT. Laparoscopic hysterectomy and bilateral adnexectomy were performed, and the histological diagnosis was endometrioid carcinoma, grade 1 (Fig. 3). Both fallopian tubes were examined in accordance with SEE-FIM protocol, and there was no tumor in them. Her germline *BRCA* status was tested by blood examination (Fig. 4) and the result was 'NM_007294.4(BRCA1):c.49G>C (p.Ala17Pro)'. The testing of *gBRCA* variant using patient's blood was performed by BRACA analysis® (Myriad Genetics, Inc.). To date, there has been no report of a clinical case with this variant type in the *BRCA1* gene. Thus, we referred to the *in-vitro* report using cultured cell lines in which the above-mentioned variant led to 'loss-of-function' (4). We also referred to the internal datum provided by Myriad Genetics, Inc., which evaluated this variant as 'suspected deleterious' (data not shown). We also considered that she had bilateral breast cancer in an asynchronistic manner under 50 years old, and her mother had breast cancer when she was 38 years old. Thus, we classified the variant as 'likely pathogenic'. She was diagnosed with HBOC and endometrial cancer, pT1ANxM0. Then chemotherapy was performed for breast cancer. She showed no recurrence of breast or endometrial cancer for 16 months after gynecologic surgery.

Table I. Relevant clinical information of the present patient.

Parameter	Value
Body mass index, kg/m^2	20.6
Irregular menstruation	No
Menarche age, years	12
First birth age, years	23
Breastfeeding history	Yes
History of unopposed estrogen therapy	No
History of benign breast disease	No
Diabetes mellitus	No
Hypertension	No
Drinking history	Opportunity drinking
Smoking history	No
Family history of colorectal cancer	No

Discussion

HBOC syndrome is becoming a more common term because of the following reasons. There were approximately 2.3 million new breast cancer cases and 685,000 breast cancer deaths worldwide in 2020 (5). Approximately 314,000 new ovarian cancer cases and 207,000 deaths occurred globally in 2020 (6). Among patients with breast cancers between 35 and 64 years old in the USA, 2.4 and 2.3% carried deleterious mutations in *BRCA1* and *BRCA2*, respectively (2). Among patients with ovarian cancer, 15% had mutations in *BRCA1* or *BRCA2* (3). In Japan, all patients with breast cancer and ovarian cancer are recommended to undergo a germline *BRCA* test. Patients with a *BRCA* variant are candidates for treatment using PARP inhibitors (7).

In the current case, the uncharacterized variant 'NM_007294.3(BRCA1):c.49G>C (p.Ala17Pro)' was detected. According to the ClinVar database, the interpretation of this variant is not provided. We found only one *in-vitro* report about this variant in the *BRCA1* gene (4). Several variants were generated and characterized *in vitro* and this variant was one of them. The saturation genome editing assay for *BRCA1* NM_007294.3:c.49G>C, a missense variant, revealed that this variant corresponds with the 'loss-of-function' mutation (4). We also referred to the internal datum provided by Myriad Genetics, Inc., which classified this variant as 'suspected deleterious'. We considered that she had bilateral breast cancer in an asynchronistic manner under 50 years old, and her mother had breast cancer at the age of 38. *In silico* prediction tools revealed that the SIFT score was 0.00, corresponding to 'deleterious', and the PolyPhen-2 score was 0.896, corresponding to 'possibly damaging'. We also recognized that a clinical decision should not be based solely on *in silico* prediction tools (8), but should consider multiple factors, including past history, family history, references from a database such as ClinVar, etc. Thus, we classified the variant as 'likely pathogenic'. In this variant, the amino acid of alanine mutates to proline. We speculate that this mutation may alter the secondary structure and the function of protein because proline generally produces not α-helix or β-sheet, but turn structure of protein. She was diagnosed with HBOC syndrome and endometrial cancer, pT1ANxM0. Then chemotherapy was performed to treat her breast cancer.

Patients with HBOC syndrome may also have an increased risk of other types of cancer, including pancreatic cancer, prostate cancer, and melanoma (1). However, the association between endometrial cancer and *BRCA1/2* genes is unresolved, and the risk elevation of endometrial cancer in HBOC patients is not understood. There is a report of an international cohort study about the incidence of endometrial cancer in women with *BRCA1* and *BRCA2* mutations (9). Segev *et al* followed 4,456 women with *BRCA1* (n=3536) and *BRCA2* (n=920) mutations (9). After 5.7 years follow-up, 17 endometrial cancer cases (13 cases in *BRCA1* and 4 cases in *BRCA2*) were identified. They concluded that the risk of endometrial cancer is higher in *BRCA1* mutation carrier than in the general population, and the excessive risk largely attributable to a history of tamoxifen use (9). De Jonge *et al* (10) investigated *gBRCA*-associated endometrial cancer. They reported that *gBRCA*-associated endometrial carcinomas were more frequently non-endometroid and grade 3 histology compare with sporadic endometrial carcinomas. They also reported that sporadic endometrial cancer cases were mostly grade 1 endometroid carcinoma. They concluded that endometrial cancer is linked with *gBRCA*-associated HBOC syndrome, and *gBRCA*-associated endometrial cancer is associated with unfavorable clinical outcomes (10). Vietri *et al* (11) examined 40 patients with endometrial cancer, 19 belonging to families with Lynch syndrome and 21 related to HBOC. They performed mutation analysis of *MLH1*, *MSH2*, *BRCA1*, and *BRCA2*. Out of the 19 patients belonging to Lynch syndrome families, 8 showed pathogenic variants. Out of the 21 patients belonging to HBOC

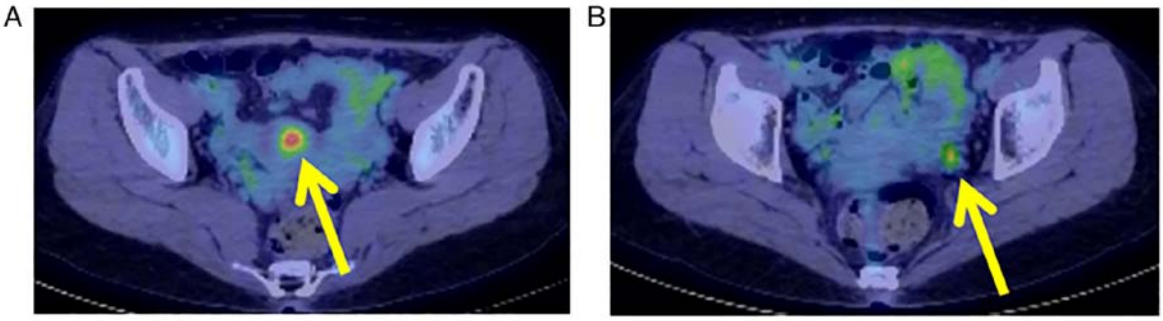

Figure 1. Positron emission tomography/computed tomography in the (A) endometrium and (B) left ovary revealed a high fluorodeoxyglucose uptake (maximum standardized uptake value, 4.87 and 3.22, respectively). The arrows indicate endometrium (A) and left ovary (B), respectively.

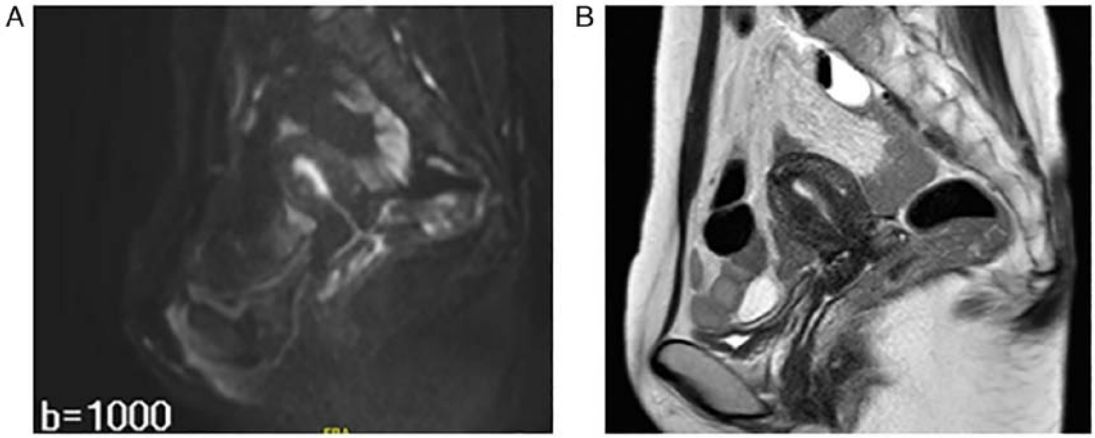

Figure 2. MRI results. (A) MRI diffusion-weighted image (b=1,000) revealing a high intensity in the endometrium, whereas (B) the myometrial invasion was not observed in the T2-weighted image.

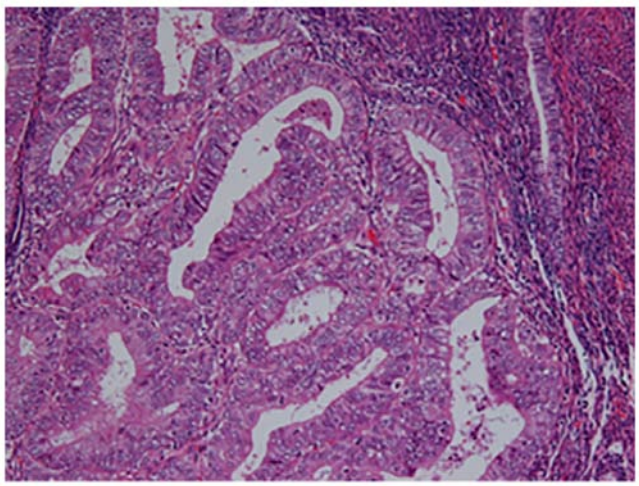

Figure 3. Histological diagnosis was endometrial carcinoma, grade 1. Nuclear enlargement, hyperchromatism and nucleoli enlargement were detected in proliferated atypical glands. The cribriform pattern was also noted. Hematoxylin and eosin staining. Magnification, x40.

Figure 4. Germline BRCA test (BRACA analysis®) indicating a result of 'NM_007294.4(BRCA1):c.49G>C (p.Ala17Pro)'.

families, 9 showed pathogenic variants. They found that patients with hereditary endometrial cancers have a high percentage of mutations in the susceptible genes associated with Lynch syndrome and HBOC, and examination for endometrial cancer should be recommended for patients with HBOC.

We examined a case with HBOC syndrome and an uncharacterized variant in the *BRCA1* gene in a patient with endometrial cancer after surgery for bilateral breast cancer. For this report, we could not obtain much information regarding the variant. The relationship between HBOC syndrome and endometrial cancer is unresolved, although endometrial cancer in HBOC patients is considered pathologically high-grade and is associated with poor clinical outcomes according to the literature (10). In cases of breast cancer associated with HBOC syndrome, the hormone receptor is often negative, and many cases were not tested for endometrial cancer. Gynecologists and breast surgeons should recognize the risk of endometrial cancer associated with HBOC syndrome, and we suggest that HBOC patients undergo screening for endometrial cancer.

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Availability of data and materials

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YM, YH, SM, NO and KI participated in the conception and design of the study. YM, SM and NO obtained the data and treated the patient. YM analyzed the data and drafted the manuscript. YH analyzed the data by the bioinformatic methods. KI revised the manuscript prior to submission. In addition, KI and YM were major contributors in designing the study. YM and KI confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of any associated data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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